EURASIAN ECONOMIC COMMISSION
COUNCIL

RESOLUTION

November 03, 2016. **No78** Astana city

On the Rules of marketing authorization and assessment of medicinal products for medical use

(as amended by Decision of the Council of the Eurasian Economic Commission No. 55 dated 14.06.2018)

In accordance with Article 7 of the Agreement on common principles and rules of medicinal products circulation within the Eurasian Economic Union dated on December 23, 2014, clause 84 Annex # 1 to the Regulations of the work of the Eurasian Economic Commission, approved by the Resolution of the Supreme Eurasian Economic Council of December 23, 2014 # 98, and the Resolution of the Supreme Eurasian Economic Council of December 23, 2014 # 108 "On the implementation of the Agreement on common principles and rules of medicinal products circulation in the Eurasian Economic Union" the Council of the Eurasian Economic Commission **has resolved** the following**:**

1. Approve the enclosed Rules of marketing authorization and assessment of medical products for medical use (hereinafter - the Rules).

2. Establish that:

a) marketing authorization, confirmation (renewal) of the marketing authorization, variations to the marketing authorization application dossier and other procedures related to the marketing authorization of medicinal products for medical use, provided for by the laws of the member states of the Eurasian Economic Union (hereinafter referred to as the Member States, the Union), and not completed by the authorized bodies of the Member States before January 1, 2016 shall be carried out in accordance with the laws of the Member States;

b) before December 31, 2020, at the discretion of the applicant, marketing authorization of the medicinal product can take place either in accordance with the Rules or in accordance with the legislation of the Member State. At the same, the medicinal products authorized in accordance with the legislation of a Member State shall be permitted for circulation only at the territory of the Member State whose authorities issued the marketing authorization;

c) the validity of marketing authorizations issued by authorities of the Member States before January 1, 2016 may be extended in accordance with the laws of the Member States, but not longer than until December 31, 2025. At the same time, any variations in the marketing authorization application dossier of medicinal product formed in accordance with the laws of the Member States shall be carried out in accordance with the laws of the Member States but not later than on December 31, 2025;

d) medicinal products authorized under the laws of the Member States should be brought into compliance with the requirements of international treaties and acts of the Union Law by December 31, 2025;

e) certificates of marketing authorization for a medicinal products issued in accordance with the laws of the Member States shall be valid until the expiry of their validity but not later than December 31, 2025.

3. The Member States shall up to December 31, 2016:

a) approve the fees (charges) or other mandatory payments stipulated by the Rules, taking into account the complexity of the procedures and the scope of work performed in the reference state and the states of recognition, including:

in case of marketing authorization of the medical product;

in case of confirmation (renewal) of marketing authorization of the medical product;

in case of bringing the marketing authorization dossier for the medical product in line with the requirements of international treaties and acts of the Union Law;

b) determine the bodies (organizations) authorized for implementation of marketing authorization, confirmation (renewal) of marketing authorization, variation to the marketing authorization application dossier and the other procedures related to the marketing authorization of medicinal products provided for by the Rules, and inform the Eurasian Economic Commission thereof.

4. This Resolution shall enter into force after 10 calendar days from the date of entry into force of the Protocol signed on December 2, 2015, on accession of the Republic of Armenia to the Agreement on Common principles and rules of medicinal products circulation in the Eurasian Economic Union dated on December 23, 2014, but not earlier than 10 calendar days from the date of official publication of this Resolution.

Members of the Board of the Eurasian Economic Commission:

From the Republic of Armenia	From the Republic of Belarus	From the Republic of Kazakhstan	From the Republic of Kyrgyzstan	From the Russian Federation
V. Gabrielyan	**V. Matyuschevsky**	**A. Mamin**	**O. Pankratov**	**I. Shuvalov**

ADOPTED
by Decision of the Council of
the Eurasian Economic Commission
No 78 of 3 November 2016

RULES
of authorization and assessment of medicinal products for human use

I. GENERAL PROVISIONS

1. In view of forming the Common market in the Eurasian Economic Union of medicinal products for human use, these Rules shall establish a procedure for granting a marketing authorization, confirmation (renewal) of the marketing authorization, variation to the marketing authorization and assessment of medicinal products for human use (hereinafter referred to as the Union), as well as for other procedures related to the marketing authorization for medicinal products for human use (hereinafter referred to as authorization-related procedures) including:

a) bringing a marketing authorization dossier of a medicinal product authorized in the Member States of the Union (hereinafter referred to as the Member States) before the Agreement on Common Principles and Rules Governing Medicinal Products within the Union of 23 December 2014 (hereinafter referred to as the Agreement) came into effect and up until 31 December 2020, into compliance with these Rules (hereinafter referred to as bringing into compliance with the requirements of the Union);

b) suspension or withdrawal of a marketing authorization for the medicinal products or restriction of use thereof;

c) issuance of a replacement document for a certificate of marketing authorization for a medicinal product.

2. The requirements of these Rules shall apply to developers and manufacturers of medicinal products, marketing authorization holders, their representatives, medicines competent authorities and assessment organizations.

3. The requirements of these Rules do not apply to:

a) medicinal products intended for use during warfare, emergencies, for prevention and treatment of diseases and injuries due to release of chemical, biological, radiation hazards, and developed under the order of the Member States competent authorities for safety and defense and whose circulation is regulated by the Member States legislation;

b) medicinal products for veterinary use and whose circulation is regulated by other acts which constitute the law of the Union.

4. The medicinal products intended for marketing within the Common Market of the Union or within any Member State(s) are subject to marketing authorization in accordance with these Rules.

5. The following products are not subject to marketing authorization in accordance with these Rules in the Union:

a) medicinal products prepared in pharmacies;

b) active pharmaceutical ingredients (active substances);

c) medicinal products for use in non-clinical and clinical studies;

d) medicinal products imported by individuals for personal use;

e) radiopharmaceuticals prepared directly in healthcare institutions in accordance with the procedure established by the competent authorities;

f) medicinal products not to be marketed within the Customs territory of the Union;

g) samples of medicinal products intended for use during marketing authorization procedure and reference standards;

h) medicinal products intended for use as a showpiece.

6. If a medicinal product is recognized as an orphan medicinal product within of all, or some of, the Member States pursuant to the Member States legislation, such a medicinal product is subject to marketing authorization pursuant to sections V and VII or sections VI and VII of these Rules and in compliance with the provisions of Section 16 of Part III of Appendix 1 to these Rules.

If a medicinal product is not recognized as an orphan medicinal product within any Member State pursuant to its legislation, such a medicinal product is subject to marketing authorization in this Member State pursuant to the provisions of Subsection I of Section V of these Rules and Appendix 1 to these Rules.

7. The granting a marketing authorization for medicinal products having different qualitative composition of its active substances using the same brand name is prohibited.

8. A medicinal product may be authorized using different brand names in different Member States in the following cases:

a) use of a proposed brand name is allegedly illegal and is against moral principles or otherwise does not consider the cultural and/or language nuances;

b) intellectual rights for a brand name in the form of trademark belong to a subject different from the medicinal product marketing authorization applicant (hereinafter referred to as applicant) or the marketing authorization holder, and such an applicant or marketing authorization holder does not provide an appropriate license agreement authorizing the use of the trademark;

c) the medicinal product was authorized for marketing under different brand names pursuant to the law of the Member States before 31 December 2020.

9. A medicinal product marketing authorization, confirmation (renewal) of the marketing authorization, variation to the marketing authorization and other procedures related to the marketing authorization for medicinal products shall be carried out by the competent authorities.

10. The assessment of a medicinal product shall be carried out by the assessment organization as laid down in the Member State legislation.

11. In the course of the granting a marketing authorization for, or assessment of, medicinal products, competent authorities and assessment organizations shall ensure the confidentiality of the information contained in the marketing authorization application dossier of the medicinal product including the information in the closed part of the active substance master file.

The Eurasian Economic Commission (hereinafter referred to as the Commission) or the Expert Committee for Medicinal Products (hereinafter referred to as the Expert Committee) shall ensure confidentiality of the information contained in the marketing authorization application dossier of the medicinal product accessed by it in the course of performing its duties.

12. The applicant shall pay a fee for the granting a marketing authorization, confirmation (renewal) of the marketing authorization, variation to the marketing authorization and assessment of medicinal products, and procedures related to the marketing authorization and for inspections performed to verify compliance with the requirements of the Good Pharmaceutical Practices and initiated under the aforementioned procedures.

13. The fees payable referred to in paragraph 12 of these Rules are not to be refunded to the applicant.

14. Upon receiving an application for a marketing authorization, confirmation (renewal) of the marketing authorization, variation to the marketing authorization, or authorization-related procedures, the competent authority (assessment organization) of the reference Member State shall assign a unique application number generated using the Integrated Union Information System (hereinafter referred to as the Integrated System) to the application and communicate the number assigned to the applicant.

15. A competent authority (assessment organization) of the Member State shall submit the information related to the marketing authorization, confirmation (renewal) of the marketing authorization, variation to the marketing authorization or authorization-related procedures to the competent authorities (assessment organizations) of the Member States concerned and to the Commission via the Integrated System using the application number as laid down in the Procedure for establishing and maintaining the Common Register of the Authorized Medicinal Products (hereinafter referred to as the Common Register).

On request of the competent authorities (assessment organizations) of the Member States concerned, the competent authority (assessment organization) of the reference Member State shall provide an access to the information in the marketing authorization application dossier via the Integrated System within 5 business days beginning with the day the marketing authorization application dossier is electronically submitted by the applicant.

16. Having authorized a medicinal product, the competent authority of each Member State which has authorized the medicinal product shall issue a certificate of marketing authorization for a medicinal product serving as an evidence of the marketing authorization.

17. A certificate of marketing authorization for a medicinal product shall be issued by the competent authority which has authorized the medicinal product using a single form and as laid down in the Rules of completion of a certificate of marketing authorization for a medicinal product for human use set by Appendix 17 to these Rules.

Where a certificate of marketing authorization for a medicinal product is lost or damaged, the competent authority which has issued the certificate of marketing authorization shall issue the replacement of that lost or damaged certificate completed as laid down in Appendix 17 to these Rules in response to the marketing authorization holder's application for replacement of the certificate of marketing authorization for a medicinal product.

18. The marketing authorization certificate issued for the first time shall be valid for 5 years in the reference Member State. After the marketing authorization ceases to be valid, the marketing authorization for a medicinal product shall be granted for an unlimited period providing the marketing authorization is confirmed (renewed). In cases specified in Section VII of these Rules and in other cases related to pharmacovigilance issues, the competent authority may grant the marketing authorization valid for the next 5 years having considered the outcome of the confirmation (renewal) of the marketing authorization.

The marketing authorization for a medicinal product granted as laid down in the Member States legislation before 31 December 2020 and where the medicinal product has been marketed for at least 5 years in at least 3 Member States shall be granted for an unlimited period pursuant to the procedure for bringing into compliance with the requirements of the Union as laid down in Section XIII of these Rules.

II. DEFINITIONS

19. For the purposes of these Rules, the following terms shall bear the following meanings:

'allergen' shall mean any medicinal product which is intended to identify or induce a specific acquired alteration in the immunological response to an allergizing agent;

'medicinal product safety *(risk-benefit balance)***'** means an evaluation of the positive therapeutic effects of the medicinal product in relation to the risks associated with its use (the risk concept includes any risk relating the quality, safety, or efficacy of the medicinal product as regards to patient's health or public health);

'similar biological medicinal product *(bioanalogue, biosimilar medicinal product, biosimilar)***'** means a biological medicinal product that contains a version of the active substance of already authorized original biological medicinal product (reference medicinal product) and whose similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety, and efficacy has been demonstrated based on a comprehensive comparability exercise;

'bioavailability' means the rate and extent to which the active substance or active moiety is absorbed from a dosage form and becomes available at the site of action;

'bioequivalence' means the absence of a significant difference in the rate and extent to which the active substance or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study;

'biological medicinal product' means a medicinal product, the active substance of which produced by or extracted from a biological source and that needs for its characterization and its

quality control a combination of physico-chemical-biological testing, together with the production process and its control;

'generic medicinal product' means a medicinal product which has the same qualitative and quantitative composition in active substances and the same pharmaceutical form as the original product, and whose bioequivalence with the original medicinal product has been demonstrated by appropriate bioavailability studies. The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regard to safety and/or efficacy. The various immediate-release oral pharmaceutical forms shall be considered to be one and the same pharmaceutical form for the purposes of bioavailability studies.

'radionuclide generator' means any system incorporating a fixed parent radionuclide from which is produced a daughter radionuclide which shall be obtained by elution or by any other method and used in a radiopharmaceutical;

'hybrid medicinal product' means a medicinal product which does not fall within the definition of a generic medicinal product since its bioequivalence cannot be demonstrated through bioavailability studies or in case of changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration, vis-à-vis the reference medicinal product;

'homeopathic medicinal product' means a medicinal product prepared from homeopathic stocks in accordance with a homeopathic manufacturing procedure described by the Union Pharmacopoeia or, in the absence thereof, by homeopathic pharmacopoeias;

'Member State concerned' means a Member State where a medicinal product has been authorized (or is being authorized) based on the outcome of the assessment including evaluation of an assessment report on the medicinal product's safety, efficacy, and quality drawn up by the reference Member State;

'marketing authorization holder' means a legal entity to whom a medicinal product marketing authorization has been granted and which is legally responsible for the safety, efficacy, and quality of the medicinal product;

'Common Register of the Authorized Medicinal Products' means a single information resource established within the Integration System and containing information on medicinal products authorized or being subjected to other authorization-related procedures under these Rules;

'applicant' means a legal entity authorized to submit the application for marketing authorization, confirmation (renewal) of the marketing authorization, variation to the marketing authorization, or other authorization-related procedures and responsible for the reliability of the information contained in the documents and the particulars of the marketing authorization application dossier submitted;

'immunological medicinal product *(immunobiological medicinal product)***'** means a medicinal product intended to produce active immunity or passive immunity, or diagnose the state of immunity, or diagnose/produce specific acquired alteration in the immunological response to an allergizing agents;

"patient leaflet *(package leaflet)***"** means a document containing information for the user which accompanies the medicinal product and is put in the package and approved by the competent authority of the Member State as laid down in the legal acts of the Union's authorities;

'quality of the medicinal product' means a set of the attributes and characteristics of an active substance or medicinal product needed for the suitability for its intended use as laid down in the legal acts of the Union's authorities;

'dosage form' means a state of medicinal product according to the routes of its administration and use and furnishing the achievement of the necessary effect;

'herbal substances' mean whole or fragmented plants, algae, fungi or lichen or parts thereof in fresh or dried form used to manufacture medicinal products;

'well established medicinal product' means a medicinal product whose active substance has been in well-established medicinal use for at least ten years from the first systematic and documented use of that active substance(s) as a medicinal product within at least 3 Member

States, with recognized efficacy and an acceptable level of safety documented by detailed bibliographic reference to the results of post marketing studies and/or epidemiological studies;

'herbal medicinal product' means a medicinal product, exclusively containing as active ingredients one or more herbal substances and/or one or more herbal preparations;

'international non-proprietary name' means a name of an active substance recommended by the World Health Organization;

'normative document' means a document establishing requirements for the quality control of a medicinal product (it contains a specification and a description of analytical procedures and tests or references thereon, as well as appropriate acceptance criteria for the specified quality attributes, etc.) based on the assessment of the medicinal product. It is approved by the competent authority upon granting a marketing authorization for the medicinal product in the Union and is intended for post-marketing quality control of the medicinal product in the Union;

'summary of product characteristics' means a document containing the information intended for healthcare professionals about safe and efficacious use of the medicinal product and approved by the competent authority of the Member State as laid down in the legal acts of the Union's authorities;

'common name' means a name of a medicinal product which does not have an international non-proprietary name, or of a combination of medicinal products, used to unite them into one group under the single name based on the same qualitative composition of its active substances;

'original medicinal product' means a medicinal product containing a new active substance which has been authorized and placed to the global pharmaceutical market for the first time based on a dossier containing the results of full preclinical (non-clinical) studies and clinical trials which demonstrate the quality, safety, and efficacy thereof;

'orphan (rare) medicinal product' means a medicinal product intended for the diagnosis, ethiopathogenetic or pathogenetic treatment (treatment altering a mechanism of disease development) of rare (orphan) diseases the frequency of which does not exceed officially established level in the Member State;

'representative of the marketing authorization holder' means the legal entity established as laid down in the Member State legislation or a stand-alone department of the legal entity located in the Member State and designated by the marketing authorization holder to take actions related to the circulation of medicinal products in the Member State concerned;

'manufacturer of medicinal products' means a company carrying out any activities related to the manufacturing of pharmaceuticals and holding an authorization (a license) for such activities issued by the competent authority of the manufacturer's own country;

'radiopharmaceutical' means a medicinal product which, when ready for use, contains one or more radionuclides (radioactive isotopes) as an active substance or as a component of the active substance;

'herbal preparation' means preparation obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices, and processed exudates;

'marketing authorization application dossier' means a set of documents (including the application) to be drawn up as laid down in these Rules and submitted to carry out procedures related to authorization, confirmation (renewal) of the marketing authorization of the medicinal product;

'certificate of marketing authorization for a medicinal product' means a document drawn up using a single template issued by a competent authority and which confirms the authorization of the medicinal product and approves its medical use within the Member State;

'authorization number' means a code designation assigned to a medicinal product after the authorization had been granted in a Member State;

'authorization of a medicinal product' means a process of granting the authorization for the medical use of the medicinal product within one or more Member States performed as laid down in these Rules;

‘reference Member State’ means a Member State which is responsible for drawing up an assessment report on the safety, efficacy, and quality of a medicinal product based on the outcome of assessment of the medicinal product as laid down in these Rules;

“reference medicinal product” means a medicinal product used as a reference and against which the characteristics of the medicinal product concerned are determined (compared);

‘risks associated with the use of a medicinal product’ mean any risks relating to the quality, safety, or efficacy of a medicinal product as regards patients’ health or public health or any risks of undesirable effects on the environment;

‘specification’ means a list of tests (quality attributes), references to analytical procedures and tests, and acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described;

‘reference standard’ means an identified homogenous substance or a mixture of substances intended to be used in chemical, physical, or biological tests where its properties are compared with the properties of the test material, and is of sufficient degree of purity for the intended use;

‘brand name of a medicinal product’ means the name of the medicinal product under which the medicinal product has been authorized;

‘active substance (active pharmaceutical ingredient)’ means a pharmaceutical intended for the manufacture or preparation of medicinal products;

‘assessment report on the safety, efficacy, and quality *(assessment report)***’** means a document containing the results of evaluation of the safety, efficacy, and quality of a medicinal product and the opinion on its marketing authorization, confirmation (renewal) of the marketing authorization, variation to the marketing authorization, or bringing into compliance with the requirements of the Union and drawn up by the assessment organization of the reference Member State;

‘efficacy of a medicinal product’ means a set of characteristics furnishing a prophylactic, diagnostic or treatment effect or restoring, correcting or modifying of a physiological function.

III. GENERAL PRINCIPLES OF MARKETING AUTHORIZATION FOR MEDICINAL PRODUCTS

20. A marketing authorization for medicinal products may be granted at the request of an applicant in several Member States in accordance with the mutual recognition procedure successively or in the several Member States in accordance with the decentralized marketing authorization procedure simultaneously.

21. The mutual recognition procedure shall be carried out:

a) by the reference Member State under these Rules in view of granting a marketing authorization for a medicinal product only in this Member State (the national marketing authorization procedure);

b) in the Member States concerned as desired by the applicant after the marketing authorization for the medicinal product has been granted in the reference Member State under the mutual recognition procedure.

22. The decentralized marketing authorization procedure shall be carried out simultaneously by several Member States where the application for the marketing authorization has been submitted and the reference Member State is need to be chosen.

23. The applicant may chose the reference Member State and, where necessary, the Member State concerned when submitting the application for granting a marketing authorization for a medicinal product.

24. Only one Member State may be designated as a reference Member State.

25. The requirements for the documents and particulars to be included in the marketing authorization application dossier in the Common Technical Document format which is to be provided for granting a marketing authorization for a medicinal product are provided in Appendices 1 to 5 to these Rules.

26. Before the application for granting a marketing authorization for a medicinal product is submitted and upon applicant’s request, competent authorities or assessment organizations of the Member States may give a scientific or pre-marketing advice as laid down in the Member States

legislation to cover the issues related to test procedures, pre-clinical and clinical trials (tests), nuances of granting a marketing authorization including qualification of the type of an application with the view of determining the extent of the documents and particulars needed in the marketing authorization application dossier from the perspective of its completeness, to determine contact persons in the Member States concerned, and the way of submitting the application and marketing authorization application dossier, to determine the need of the samples of a finished product, reference standards, materials, specific reagents, and consumables necessary for the verification of test procedures in the assessment organization's laboratory or by its appointment, and other questions.

27. The competent authority or assessment organization of the reference Member State shall initiate the inspection by the Member State pharmaceutical inspectorate to verify compliance with the requirements of the respective pharmaceutical practices if there is any evidence prejudicing the reliability of the information provided by the applicant in the marketing authorization application dossier as regards to the non-clinical (preclinical) and clinical trials (tests) of a medicinal product or the manufacturing thereof including the manufacturing of the active substance or the management of a pharmacovigilance system within granting a marketing authorization, confirmation (renewal) of the marketing authorization, variation to the marketing authorization or authorization-related procedures. These inspections may be initiated in cases referred to in paragraphs 31, 33, 35, 37 to 39 of these Rules. The competent authority of the reference Member State is responsible for timely initiation of the respective unscheduled inspections where necessary.

28. The manufacturing of medicinal products shall comply with the requirements of the Good Manufacturing Practice of the Eurasian Economic Union.

29. When submitting an application for granting a marketing authorization, confirmation (renewal) of the marketing authorization, bringing into compliance with the Union's requirements, the applicant shall provide a valid document in the marketing authorization application dossier confirming compliance with the requirements of the Good Manufacturing Practice of the Union for the manufacturing site(s) where the finished product is manufactured and release testing of the finished product are carried out in respect of the medicinal product applied for the marketing authorization, confirmation (renewal) of the marketing authorization or bringing into compliance with the requirements of the Union.

Up until 31 December 2020, in the absence of the document confirming compliance with the requirements of the Good Manufacturing Practice of the Union, an applicant may provide a document confirming compliance of the manufacturing site(s) where the finished product is manufactured and release testing is carried out with the requirements of the Good Manufacturing Practice issued to the medicinal product manufacturer by the competent authority of the Member State.

30. If it is not possible to provide a valid document confirming compliance with the requirements of the Good Manufacturing Practice of the Union for (a) medicinal product manufacturing site(s), the applicant, when submitting the application for a marketing authorization for a medicinal product or bringing into compliance with the requirements of the Union before 31 December 2020, shall submit the following documents and information instead of the aforementioned document:

a) valid documents confirming compliance of the manufacturing site(s) carrying out manufacturing activities in respect of a finished product and release testing with the requirements of the Good Manufacturing Practice issued to the medicinal product manufacturer by the competent authority of the medicinal product manufacturer's own country;

b) the copy of the latest inspection report for the manufacturing site(s) issued by the competent authority of the manufacturer's own country and/or other competent authority within the previous 3 years;

c) information on the outcome of all inspections of this/these manufacturing site(s) for compliance with the requirements of the Good Manufacturing Practice carried out within the previous 3 years;

d) the information on complaints concerning the quality of the medicinal products manufactured at this manufacturing site(s) within the previous 3 years;

e) the consent to be a subject of a pharmaceutical inspection for compliance with the requirements of the Good Manufacturing Practice of the Union;

f) the copy of the site master file(s);

31. Based on the documents submitted by an applicant and referred to in paragraph 30 of these Rules and taking into account the assessment of the potential risks, the reference Member State shall make a decision whether to carry out an unscheduled pharmaceutical inspection for compliance with the requirements of the Good Manufacturing Practice of the Union within the procedure of granting a marketing authorization for a medicinal product or to put an inspection of the manufacturing site(s) where the medicinal product (including the active substance as appropriate) applied for marketing authorization is manufactured or for bringing into compliance with the requirements of the Union, in the inspection plan for the next 3 years upon granting a marketing authorization.

32. If the competent authority of the reference Member State acknowledges in writing failure to carry out the inspection of the manufacturing site(s) within granting a marketing authorization for a medicinal product, the applicant may, subject to agreement of the reference Member State, refer the application for inspection of this/these manufacturing site(s) for compliance with the requirements of the Good Manufacturing Practice of the Union to another Member State.

Where the competent authorities of the Member State concerned refuse in writing to carry out an unscheduled inspection of the medicinal product manufacturing site(s), the competent authority of the reference Member State must plan and carry out the unscheduled inspection within granting a marketing authorization for a medicinal product.

33. A decision whether to carry out an unscheduled pharmaceutical inspection for compliance with the requirements of the Good Manufacturing Practice of the Union shall be made by the competent authority of the reference Member State within the following procedures:

a) granting a marketing authorization – in case of medicinal products manufactured at sites manufacturing a finished product and carrying out release testing which were not previously inspected by the competent authority (assessment organization) of at least one Member State;

b) procedure for bringing into compliance with the requirements of the Union's – for the medicinal products previously authorized in the Member States if the manufacturing site(s) is(are) specified (introduced, replaced) which has(have) not been previously inspected by the competent authority (assessment organization) of at least one Member State.

34. Non-clinical safety studies of medicinal products shall be conducted in accordance with the requirements of the Good Laboratory Practice of the Union subject to approval by the Commission.

Clinical trials of medicinal products shall be conducted in accordance with the requirements of the Good Clinical Practice of the Union subject to approval by the Commission.

35. Non-clinical safety studies of medicinal products manufactured in the countries which are not Members States of the Union shall be taken into account within the assessment of the medicinal product if they have been designed, implemented, and reported in accordance with the requirements of the Good Laboratory Practice which equivalent (or not inferior) to the provisions of the Union.

Clinical studies of medicinal products manufactured in the countries which are not the Members States of the Union are taken into account within the assessment of the medicinal product if they have been designed, implemented, and reported in accordance with the requirements of the Good Clinical Practice which equivalent (or not inferior) to the provisions of the Union and the principles of the World Medical Association Declaration of Helsinki - *Ethical Principles for Medical Research Involving Human Subjects*.

The competent authority of the reference Member State may trigger an unscheduled inspection for compliance with the Rules of Good Laboratory Practice of the Union within the assessment of a medicinal product if:

- evidence prejudicing reliability of the non-clinical data is revealed within the assessment of the medicinal product;

- inconclusive (medically or biologically unlikely or conflicting) study results are obtained; or

- any other circumstances provided in the Rules of the Pharmaceutical Inspections subject to approval by the Commission are discovered.

36. Within the procedure of granting a marketing authorization for a medicinal product, the clinical study reports included in the Module 5 of the marketing authorization application dossier shall be taken into account in the assessment subject to either of the following conditions:

- the clinical trials had been conducted in compliance with the Member States legislation and within their territory before 1 January 2016 (based on the date of the last visit of the last patient (volunteer)) or were being conducted as of 1 January 2016 (the recruitment of the patients (volunteers) into those studies should have been completed by this date);

- the clinical trials had been conducted in part or fully within the countries of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) before 1 January 2016 (based on the date of the last visit of the last patient (volunteer)) based on which the medicinal product has been authorized for marketing in the countries of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH);

- clinical trials commenced after 1 January 2016 have been conducted in compliance with the international agreements and acts which constitute the law of the Union and at least one clinical study has been conducted fully or in part (as regards of data obtained from the study subjects) within the Union.

If the requirements referred to in the second to fourth subparagraphs of this paragraph are not complied with, before applying for the marketing authorization for a medicinal product, the applicant must conduct clinical trials (at least one trial at the applicant's disposal and as agreed with the competent authority) fully or in part within the Union, or the competent authority shall trigger an unscheduled inspection of one clinical trial site where the trial has been conducted, within the assessment of the marketing authorization application dossier.

This paragraph does not apply to orphan medicinal products.

37. The competent authority of the reference Member State based on the documents and particulars provided by the applicant and taking into account the assessment of the potential risks shall make a decision whether to carry out an unscheduled inspection of the clinical trials of a medicinal product including bioequivalence studies for compliance with the requirements of the Good Clinical Practice of the Union within the procedure of granting a marketing authorization for a medicinal product or to put an inspection of the clinical trial in the inspection plan for the next 3 years upon granting the marketing authorization. In the latter case a scheduled inspection shall be carried out at least one clinical trial site in compliance with the Rules of the Pharmaceutical Inspections subject to approval by the Commission.

38. A decision on an unscheduled inspection of a clinical trial for compliance with the requirements of the Good Clinical Practice of the Union (or for compliance with the requirements of the Good Laboratory Practice of the Union as appropriate) shall be made by the competent authority based on the consideration of all of the following:

- absence of the information on the Independent Ethics Committee's approval of a clinical study;

- violations during obtaining informed consent or information to be provided to the study participants are revealed;

- there were issues related to the administrative structure of the clinical study (lack or ambiguity of the information);

- there were substantial amendments not specified in the protocol during the trial which violate the requirements of the Rules of the Good Clinical Practice subject to the approval by the Commission;

- absence of, or insufficient information on, the measurement of the efficacy and/or safety parameters (in respect of sampling, identification, processing of the clinical trial samples, assay conditions) in the clinical study protocol and report;

- there is indication on exclusion of the data on study subjects from the statistical analysis without any justification;

- there is evidence prejudicing reliability of the data on clinical studies of the medicinal product included in the marketing authorization application dossier (unjustified or unclear

differences between the efficacy and safety endpoints in the clinical study protocol and report; inconsistency, inaccuracy, or incompleteness of data recording; protocol amendments are not reflected in other documents of the clinical study, multiple missing data which might affect statistical power of the study);

- implausible or inappropriate clinical data (conflicting data compared to known data of other studies, low reporting rate of serious adverse reactions and/or implausible data in favor of the investigational product compared to the results obtained by other investigators or in other studies, medically or biologically unlikely (implausible or conflicting) results between the studies or study sites);

- critical dependence (in terms of demonstration of the product efficacy and safety and the risk-benefit balance) on a single study or a study with a small sample size;

- medicinal product is intended for use by the large population (for example, vaccines or other medicinal products intended for the simultaneous use by large populations);

- potential for ethical concerns (vulnerable populations: paediatric, mentally impaired, lack of alternative therapy, institutionalized patients, etc. provided in the Rules of the Good Clinical Practice subject to the approval by the Commission);

- the clinical study is of geographic origin where the requirements for clinical trials are inferior in comparison to those established in the Union;

- information from the competent authorities of the countries outside the Union regarding concerns with the study site or the sponsor compliance with the requirements of the Good Clinical Practice; and

- there are circumstances referred to in the Rules of the Pharmaceutical Inspections subject to approval by the Commission.

If there is any suspicion as regards to the quality of a medicinal product or reference products including placebo used in the clinical trial, a decision shall be made to carry out an inspection (unscheduled or scheduled) of the manufacturing site of the medicinal product to verify compliance with the requirements of the Good Manufacturing Practice of the Union.

39. The competent authority shall decide on whether the unscheduled inspection of the bioequivalence study data is necessary by taking into account the provision of paragraphs 37 and 38 of these Rules based on the consideration of all of the following:

a) unreasonably consistent (inconsistent) bioequivalence data;

b) the number of missing data is inconsistent with the predicted values for this active substance or method of measurement;

c) implausibility (inconsistency) of clinical, statistical, or analytical data; and

d) conflicting data between the studies in respect of the pharmacokinetic parameters or the within-subject (between-subject) variability.

40. An unscheduled inspection of the pharmacovigilance system of the marketing authorization holder within granting a marketing authorization shall be carried out in cases referred to in the Rules of the Good Pharmacovigilance Practice subject to approval by the Commission.

IV. GENERAL PRINCIPLES OF THE ASSESSMENT OF MEDICINAL PRODUCTS

41. The assessment of medicinal products shall be performed to produce scientific opinion on the quality, safety, and efficacy of medicinal products and the risk-benefit balance thereof; it may consider:

a) evaluation of the documents and particulars submitted by the applicant in the marketing authorization application dossier of a medicinal product (the dossier evaluation);

b) carrying out laboratory testing for compliance with the normative document and for the verification of the quality control test procedures;

c) drawing up an assessment report on the medicinal product by reference Member State; and

d) evaluation of the assessment report by the Member State concerned taking into account the documents and particulars contained in the marketing authorization application dossier of the medicinal product.

42. The essential principles of the assessment of medicinal products within granting a marketing authorization shall be:

a) independence and legal protection of assessors performing their professional duties;

b) adherence to the Member States legislation, international agreements, and acts which constitute the law of the Union;

c) the scientific approach, completeness, comprehensiveness, and objectivity during the assessment of materials and particulars and producing the substantiated assessment conclusions in accordance with written acceptance criteria;

d) expertise and high qualification of the assessment organizations and assessors;

e) systematic approach to the assessment of a medicinal product and to its procedures;

f) focus on the global scientific and technical progress, standards and policies for the technical and public safety;

g) openness of the assessment outcome while securing the classified information, the professional and commercial secrecy as laid down in the Member States legislation, international agreements and acts which constitute the law of the Union.

43. During the development, non-clinical (pre-clinical) and clinical trials (tests) of a medicinal product, its manufacturing, pharmacovigilance activities and drawing up the documents for the marketing authorization, confirmation (renewal) of the marketing authorization, variation to the marketing authorization and other procedures related to authorization, developers, manufacturers, and marketing authorization holders of medicinal product or their authorized representatives shall adhere to the Member States legislation, international agreements and acts which constitute the law of the Union, as well as they shall choose efficient approaches which, should they implemented, ensure the complying with such requirements and the requirements provided in the appropriate decisions and recommendations adopted by the Commission. In case of the deviation from the aforementioned recommendations, the applicant should provide justification of the acceptability of a chosen approach in respect of the medicinal product quality, efficacy, and safety. The justification provided is subject to the evaluation in the course of assessment of a medicinal product.

44. The assessment of a medicinal product is not to be interrupted for the period of unscheduled pharmaceutical inspection carried out to verify compliance with the requirements of the Good Practices of the Union (the Good Manufacturing, Laboratory, Clinical, Pharmacovigilance Practices), but the final assessment report shall be drawn up by the competent authority (assessment organization) of the reference Member State only when the outcome of the unscheduled pharmaceutical inspections are taken into account as appropriate. These inspections shall be carried out within a maximum of 180 calendar days beginning with the day the decision of the competent authority on triggering an inspection is made.

45. For medicinal products requiring additional safety monitoring in accordance with the requirements of the Good Pharmacovigilance Practice of the Union, the summary of the product characteristics (hereinafter referred to as SmPC) and medication guide (package leaflet) (hereinafter referred to as medication guide) for the medicinal product shall include the relevant statements and marks in accordance with Requirements for the Medication Guide and Summary of Product Characteristics of medicinal products for human use subject to approval by the Commission.

V. THE PROCEDURE FOR GRANTING A MARKETING AUTHORIZATION AND ASSESSMENT OF MEDICINAL PRODUCTS USING THE MUTUAL RECOGNITION PROCEDURE

V.I. Granting a marketing authorization and assessment of a medicinal product in the reference Member State

46. The granting a marketing authorization for a medicinal product and the assessment thereof in the reference Member State shall be completed within a maximum of 210 calendar days

beginning with the day an application for granting a marketing authorization for a medicinal product is submitted and up until the day a certificate of marketing authorization is issued.

47. For the purposes of granting a marketing authorization for a medicinal product, the applicant shall provide the competent authority (assessment organization) of the reference Member State with the following documents and materials:

- the application in paper and/or electronic format as laid down in Appendix 2 to these Rules;

- confirmation that the relevant fees have been paid for granting a marketing authorization for, and the assessment of, a medicinal product as required by the reference Member State legislation;

- the marketing authorization application dossier drawn up as laid down in Appendices 1 to 5 to these Rules in electronic format (Module 1 is additionally to be submitted in paper format (except for the Risk Management Plan, the manufacturing site(s) master file(s) and the pharmacovigilance master file)); and

- samples of the finished products.

The reference standards of active substances and product-related impurities, specific reagents, and other materials necessary to carry out the testing of the finished product samples specified in subparagraph five of this paragraph shall be to be provided subject to agreement with the assessment organization.

The samples of finished products, specific reagents, and other materials shall be provided in the amounts subject to agreement with the assessment organization and necessary to carry out a maximum three rounds of testing described in the normative document of a finished product or in other specifications included in the marketing authorization application dossier within the period of time subject to agreement with the competent authority (assessment organization) which is excluded from the period designated for the assessment and granting a marketing authorization for a medicinal product.

It is not necessary to provide the samples, specific reagents, and other materials when the assessment organization is incapable to carry out the tests due to the lack of the finished product samples (including the orphan, narcotic, or psychotropic medicinal products or those used to treat cost-intensive diseases due to high cost of such products), inability to ensure the appropriate conditions for transportation and/or storage of the aforementioned samples within the Member State(s) or the absence of the appropriate equipment or consumables at the disposal of the assessment organization.

48. In the circumstances referred to in the last subparagraph of paragraph 47 of these Rules, verification of analytical procedures shall to be performed at the manufacturer’s own quality control laboratory in the presence of the assessment organization’s representatives or at the manufacturer’s own contract laboratory in the presence of the assessment organization’s representatives.

49. The assessment of a medicinal product in the reference Member State shall include:

a) the verification of completeness and accuracy of format of the documents submitted in the marketing authorization application dossier;

b) evaluation of the documents and particulars provided by the applicant in the marketing authorization application dossier of a medicinal product from the perspective of its safety, efficacy, and quality;

c) carrying out laboratory testing to verify compliance with the quality requirements described in the normative document and the verification of the quality control test methods in accredited analytical laboratories;

d) triggering an unscheduled or scheduled pharmaceutical inspection as appropriate in the circumstances as laid down in these Rules; and

e) drawing up an assessment report on the medicinal product by the reference Member State.

50. The competent authority (assessment organization) of the reference Member State shall verify the completeness and accuracy of format of the documents submitted in the marketing authorization application dossier within 14 days before the assessment of the marketing authorization application dossier is started. The applicant shall be given a maximum of 90 calendar days which shall not be counted in the medicinal product assessment period to provide

the missing materials to be included in the marketing authorization application dossier in response to the observations of the competent authority (assessment organization) of the reference Member State.

51. The competent authority (assessment organization) of the reference Member State shall refuse to grant a marketing authorization for a medicinal product in case of failure to submit the marketing authorization application dossier materials in response to the observations of the competent authority (assessment organization) of the reference Member State and/or the payment of fees for the granting a marketing authorization for a medicinal product and for the assessment thereof, as required by the reference Member State legislation, is not confirmed.

52. In the course of the procedure of granting a marketing authorization for, and/or assessment of, a medicinal product, the competent authority and/or assessment organization of the reference Member State may give a notice in writing and/or in electronically requesting from the applicant to provide it with the missing additional information necessary to explain or clarify the documents or particulars provided in the marketing authorization application dossier (including proposals on amendments to the SmPC, medication guide, mock-ups of the packaging of the medicinal product, normative document or other documents of the marketing authorization application dossier). After the first request, the subsequent requests shall be acceptable only if the information provided by the applicant in response to the previous request causes to raise additional questions.

53. The period to response by the applicant to the request referred to in paragraph 52 of these Rules shall be a maximum of 90 calendar days beginning with the day the request is received.

54. As applicable and subject to the appropriate justification by the applicant, the period referred to in paragraph 53 of these Rules may be further extended by the competent authority (assessment organization) of the reference Member State. The total period for response to these requests should be a maximum of 180 calendar days.

55. The period for providing these documents requested by the competent authority (assessment organization) in the course of the assessment of the medicinal product by the applicant shall not be counted in the period of granting a marketing authorization for, and the assessment of, the medicinal product.

56. If the applicant does not provide the requested documents or particulars in due time, the assessment of, and the procedure for granting a marketing authorization for, a medicinal product shall be terminated. The applicant shall be informed on that decision of the competent authority (assessment organization) within 14 calendar days beginning with the day such a decision is made.

57. Communications between competent authorities (assessment organizations) when sending requests to the applicant shall be carried out in electronic format via the Integrated System.

58. If a pharmaceutical inspection to verify compliance with the requirements of the Good Pharmaceutical Practices of the Union is triggered, the assessment of a medicinal product shall not be suspended. In doing so, an assessment report shall be finalized only when the assessment organization has received the inspection report. An unscheduled pharmaceutical inspection together with the drawing up a report on such an inspection should be carried out within the period of the procedure of granting a marketing authorization for a medicinal product and within a maximum of 180 calendar days beginning the day the decision on triggering the inspection is made by the competent authority or assessment organization.

The applicant shall arrange a visit to the manufacturing site and/or trial site and/or marketing authorization holder’s pharmacovigilance system inspection within 30 calendar days beginning with day the information on the necessity of such an inspection is received or shall propose potential dates of the visit within 90 calendar days after the information on the necessity of such an inspection is received.

59. To draw up an assessment report, the assessment organization of the reference Member State shall draw up assessment reports on the quality aspects, on a new active substance contained in a medicinal product, on the active substance master file, on the non-clinical, clinical aspects,

the laboratory testing record (if the assessment organization has performed respective testing) using the templates provided in Appendices 6 to 10, 12, and 22 to these Rules.

60. Based on the outcome of the assessment of a medicinal product, the assessment organization of the reference Member State shall draw up a final assessment report on the medicinal product applied for a marketing authorization including the evaluation of explanations, documents, and information submitted by the applicant in response to the request of the assessment organization or competent authority using the template provided in Appendix 16 to these Rules.

61. Assessment reports on the quality, non-clinical, and clinical aspects, and a final assessment report shall be drawn up as laid down in Appendices 13 to 15 and 23 to these Rules.

62. An assessment report shall be updated by the assessment organization of the reference Member State using the procedure for variation to a marketing authorization when new information emerges which is important to the evaluation of the medicinal product quality, safety or efficacy and which may impact the medicinal product risk-benefit balance.

63. If the competent authority of the reference Member State has made a positive decision on the marketing authorization for a medicinal product based on the outcome of the assessment of the medicinal product, that competent authority within a maximum of 10 business days shall:

a) issue a certificate of marketing authorization to the applicant using the template provided in Appendix 17 to these Rules, the approved SmPC, medication guide, normative document, mock-ups of the packaging, the assessment report (where necessary the applicant shall be provided with the approved translation of the SmPC, medication guide and mock-ups of the packaging of the medicinal product into the official language of the reference Member State), the approved Risk Management Plan in the course of use of the product (as appropriate);

b) as laid down in the procedure for establishing and maintaining the Common Register, make publicly available the information on the medicinal product and the active substances contained therein in the Common Register together with the approved SmPC, medication guide, mock-ups of the packaging, normative document, and on the final assessment report drawn up as laid down in Appendix 16 to these Rules excluding the confidential data and data on assessors, on the approved Risk Management Plan in the course of use of the product medicinal product (as appropriate).

64. The competent authority of the reference Member State shall refuse to grant the marketing authorization for a medicinal product based on the outcome of the assessment in the following cases:

a) the risk-benefit balance is not considered to be favorable;

b) its therapeutic efficacy is insufficiently substantiated by the applicant;

c) the quality of the medicinal product has not been demonstrated;

d) the proposed quality control test methods are not verifiable;

e) the applicant has submitted the false information;

f) compliance with the Good Pharmaceutical Practice of the Union has not been demonstrated based on the outcome of the inspection within the procedure of granting a marketing authorization for a medicinal product.

65. Where the decision to refuse to grant the marketing authorization is made by the competent authority, the competent authority (assessment organization) of the reference Member State shall notice the applicant electronically and/or in writing within 10 days beginning with the day such a decision is made.

V.II. Granting a marketing authorization and assessment of a medicinal product in the Member State(s) concerned

66. Having a marketing authorization been granted for a medicinal product in the reference Member State, the applicant may apply for the marketing authorization using the mutual recognition procedure in other Member States chosen by the applicant as Member States concerned by submitting to the competent authorities (assessment organization) of such Member States the following:

- an application for granting a marketing authorization for a medicinal product using the mutual recognition procedure in paper and/or electronic format completed as laid down in Appendix 2 to these Rules;

- confirmation that the relevant fees have been paid for granting a marketing authorization for, and the assessment of, a medicinal product as laid down in the Member State concerned legislation; and

- Module 1 of the marketing authorization application dossier in electronic format.

If the respective requirements exist in the Member State legislation, the SmPC, medication guide, and mock-ups of the packaging of the medicinal product shall be submitted in the official language of the Member State concerned.

67. The competent authority (assessment organization) of the reference Member State, in response to the applicant's request, shall ensure the access to the marketing authorization application dossier for a medicinal product and assessment report is given to the competent authorities (assessment organizations) of the Member States concerned via the Integrated System including additional documents and particulars submitted by the applicant in response to the competent authority (assessment organization) of the reference Member State within 5 calendar days.

68. If the competent authorities of the Member State concerned and of the reference Member State reach an agreement and the opinion is made approving the assessment report, granting a marketing authorization for a medicinal product in the Member States concerned shall be carried out within a maximum of 90 calendar days beginning with day the access to the assessment report is received.

69. The assessment of a medicinal product under the mutual recognition procedure in the Member States concerned is carried out based on:

a) evaluation of the application and documents and particulars included in the marketing authorization application dossier;

b) evaluation of the assessment report drawn up by the assessment organization of the reference Member State.

70. The competent authority (assessment organization) of the Member State concerned shall refuse to grant a marketing authorization for a medicinal product within a maximum of 14 days beginning with the day the application is submitted under the mutual recognition procedure if that application is not in compliance with these Rules and/or the payment of fees for the granting a marketing authorization for a medicinal product and for the assessment thereof, provided by the Member State concerned legislation, is not confirmed.

71. Within the procedure of granting a marketing authorization for a medicinal product under the mutual recognition procedure, the competent authority (assessment organization) of the Member State concerned may send a request to the applicant and competent authority (assessment organization) of the reference Member State using the template provided in Appendix 18 to these Rules within a maximum of 50 calendar days beginning with the day the access to the assessment report has been granted.

72. The applicant shall response to the request of the competent authority (assessment organization) of the Member State concerned within a maximum of 90 calendar days. The period for response to the request is not to be counted in the period of granting a marketing authorization for, and the assessment of, the medicinal product. The competent authority (assessment organization) of the Member State concerned shall grant an access to the that response to the competent authority (assessment organization) of the reference Member State via the Integrated System within a maximum of 5 business days beginning with the day the response is received.

73. If the applicant does not provide the documents or particulars requested by the competent authority (assessment organization) of the Member State concerned in due time, the assessment of, and the procedure of granting a marketing authorization for, a medicinal product shall be terminated in that Member State concerned.

74. The applicant shall be informed in writing or electronically on that decision of the competent authority and/or assessment organization within 10 business days beginning with the day such a decision is made.

75. The competent authority (assessment organization) of the Member State concerned based on the outcome of the assessment of a medicinal product and within a maximum of 50 calendar days beginning with the day it receives the application for the marketing authorization of the medicinal product (where no such requests are sent to the applicant) or within a maximum of 20 calendar days beginning with the day the applicant's response to the request sent by the competent authority (assessment organization) of the Member State concerned is received shall send its opinion on approvability of the assessment report drawn up by the reference Member State to the competent authority (assessment organization) of the Member State, using the Integrated System.

76. If the competent authority of the Member State concerned has made a positive decision on granting a marketing authorization for a medicinal product based on the outcome of the assessment of the medicinal product, that competent authority within a maximum of 10 business days shall:

a) issue a certificate of marketing authorization to the applicant using the template provided in Appendix 17 to these Rules, the approved SmPC, medication guide, mock-ups of the packaging drawn up using the official language of the Member State concerned where such a requirement is provided by the Member State concerned legislation;

b) approve normative document issued by the reference Member State;

c) as laid down in the procedure for establishing and maintaining the Common Register, make publicly available the information on the medicinal product and the active substances contained therein in the Common Register together with the approved SmPC, medication guide, mock-ups of the packaging, approved Risk Management Plan in the course of use of the product medicinal product (as appropriate).

77. The competent authority of the Member State concerned shall issue a certificate of marketing authorization for a medicinal product valid within the period established by the reference Member State.

78. The granting a marketing authorization for a medicinal product already authorized in accordance with these Rules in other Member States not listed in the original application for granting a marketing authorization as Member States concerned and in the Member States joined the Union after the marketing authorization for a medicinal product had been granted shall be carried out under the mutual recognition procedure based on the evaluation of the current version of the assessment report drawn up by the assessment organization of the reference Member State.

79. If the assessment report drawn up by the assessment organization of the reference Member State cannot be recognized, the competent authority (assessment organization) of the Member State concerned shall send its opinion not approving that assessment report to the competent authority (assessment organization) of the reference Member State, of other Member States concerned taking part in the mutual recognition procedure, to the applicant, and to the Expert Committee, together with the following grounds for that opinion:

a) the risk-benefit balance is not considered to be favorable;

b) its therapeutic efficacy is insufficiently substantiated by the applicant;

c) the quality of the medicinal product has not been demonstrated;

d) the applicant has submitted false information;

e) compliance with the Good Pharmaceutical Practice of the Union has not been demonstrated based on the outcome of the inspection within the procedure of granting a marketing authorization for a medicinal product.

80. The Expert Committee shall carry out a procedure to consider the disagreement as laid down in the Rules of Procedure subject to approval by the Commission, within a maximum of 60 calendar days beginning with the day the opinion not approving the assessment report drawn up by the assessment organization of the reference Member State is received.

81. The competent authority of the Member State concerned shall refuse to grant a marketing authorization for a medicinal product if based on the outcome of the assessment of the medicinal product and upon completion of the procedure of resolving disagreement in the Expert Committee the decision is made that the data provided in the assessment report is insufficient to assure the quality, efficacy, and/or positive risk-benefit balance.

82. In case of disagreement between the competent authorities as regards of approving the assessment report and the resolving that disagreement by the Expert Committee is taking place, the competent authority of the Member State concerned which has recognized the assessment report drawn up by the assessment organization of the reference Member State shall issue a certificate of marketing authorization, approved SmPC, medication guide, mock-ups of the packaging and shall approve the Risk Management Plan in the course of use of the product (as appropriate) and the normative document before the decision of Expert Committee is made. On applicant's request, the competent authority of such a Member State concerned may postpone the issuance of the certificate of marketing authorization up until the agreement is reached between the competent authorities of other Member States concerned and of the reference Member State.

In that event, the issued certificate of marketing authorization shall be valid in that Member State concerned.

VI. GRANTING A MARKETING AUTHORIZATION AND ASSESSMENT OF A MEDICINAL PRODUCT IN THE REFERENCE MEMBER STATE AND MEMBER STATES CONCERNED USING THE DECENTRALIZED PROCEDURE

83. For the purposes of granting a marketing authorization for a medicinal product, the applicant shall choose a reference Member State and Member States concerned.

84. The granting a marketing authorization for a medicinal product and the assessment thereof shall be completed within a maximum of 210 calendar days beginning with the day the last of the applications for a marketing authorization for a medicinal product is submitted to the Member States concerned an up until the day certificates of marketing authorization are issued by the competent authorities of all Member States participating in the decentralized procedure.

85. The granting of a marketing authorization under the decentralized procedure shall consist of the following steps carried out simultaneously:

a) the granting a marketing authorization for a medicinal product in the reference Member State;

b) recognition of the assessment report and granting a marketing authorization in the Member States concerned.

86. For the purposes of granting a marketing authorization for a medicinal product, the applicant shall provide the competent authority (assessment organization) of the reference Member State with the following documents and materials:

- an application in paper and/or electronic format completed as laid down in Appendix 2 to these Rules;
- documents confirming the payment of fees for granting a marketing authorization for, and the assessment of, a medicinal product as required by the reference Member State legislation;
- the marketing authorization application dossier drawn up as laid down in Appendices 1 to 5 to these Rules in electronic format;
- samples of the finished products.

The reference standards of active substances and product-related impurities, specific reagents, and other materials necessary to carry out the testing of the finished product samples specified in subparagraph five of this paragraph shall be provided subject to agreement with the assessment organization.

The samples of finished products, specific reagents, and other materials shall be provided in the amounts subject to agreement with the assessment organization and necessary to carry out a maximum three rounds of testing described in the normative document of a medicinal product within the period of time subject to agreement with the competent authority (assessment organization) which is excluded from the period designated for assessment and granting a marketing authorization for a medicinal product.

It is not necessary to provide the samples, specific reagents, and other materials when the assessment organization is incapable to carry out the testing due to the lack of the medicinal product samples (including the orphan, narcotic, or psychotropic medicinal products or those used to treat cost-intensive diseases due to high cost of such products), inability to ensure the appropriate conditions for transportation and/or storage of the aforementioned samples within the

Member State(s) or the absence of the appropriate equipment or consumables at the disposal of the assessment organization.

87. In the circumstances referred to in the last subparagraph of paragraph 86 of these Rules, laboratory testing shall be performed at the manufacturer's own quality control laboratory in the presence of the assessment organization's representatives or at the manufacturer's own contract laboratory in the presence of the assessment organization's representatives.

88. Having submitted the documents to the competent authority (assessment organization) of the reference Member State, the applicant shall submit following items to the competent authorities (assessment organizations) of the Member States within 14 business days:

- an application in paper and/or electronic format completed as laid down in Appendix 2 to these Rules;
- Module 1 of the marketing authorization application dossier in paper and/or electronic format;
- documents confirming the payment of fees for granting a marketing authorization for, and the assessment of, a medicinal product as laid down in the Member State concerned legislation.

If the respective requirements exist in the Member State legislation, the SmPC, medication guide, and mock-ups of the packaging of the medicinal product shall be submitted in the official language of the Member State concerned.

89. The assessment of a medicinal product using the decentralized procedure in the reference Member State shall include:

a) verification of completeness and accuracy of the format of the documents submitted in the marketing authorization application dossier;

b) assessment of the documents and particulars provided by the applicant in the medicinal product marketing authorization application dossier from the perspective of its safety, efficacy, and quality;

c) carrying out laboratory testing to verify compliance with the quality requirements described in the normative document and the verification of the quality control test methods in accredited analytical laboratories;

d) triggering as appropriate an unscheduled or scheduled pharmaceutical inspection in the circumstances as laid down in these Rules;

e) drawing up an assessment report on medicinal product by the reference Member State.

90. The assessment of a medicinal product under the decentralized procedure in the Member States concerned is carried out based on:

a) evaluation of the application and documents and particulars included in the marketing authorization application dossier;

b) evaluation of the assessment report drawn up by the reference Member State.

91. The competent authority (assessment organization) of the reference Member State shall verify the completeness and accuracy of the format of the documents submitted in the marketing authorization application dossier within 14 days before the assessment of the marketing authorization application dossier is started. The applicant is given a maximum of 90 calendar days which are not to be counted in the medicinal product assessment period to provide the missing materials to be included in the marketing authorization application dossier in response to the observations of the competent authority (assessment organization) of the reference Member State.

Within 14 calendar day beginning with the day the application for the marketing authorization for a medicinal product is submitted to the reference Member State, the competent authority (assessment organization) of the reference Member State upon verification of the completeness and accuracy of the format of the documents submitted in the marketing authorization application dossier shall ensure the access to the marketing authorization application dossier for a medicinal product is given to the competent authorities (assessment organizations) of the Member States concerned participating in the decentralized procedure via Integrated System.

92. The competent authority (assessment organization) of the reference Member State shall refuse to grant a marketing authorization for a medicinal product in case of failure to submit the marketing authorization application dossier materials in response to the observations of the competent authority (assessment organization) of the reference Member State and/or the payment of fees for granting a marketing authorization for a medicinal product and for the assessment

thereof, as required by the reference Member State legislation, is not confirmed, and shall notify the applicant and the competent authorities (assessment organizations) of the Member States concerned within 5 business days beginning with the day the decision is made.

93. Within the procedure of granting a marketing authorization for, and/or assessment of, a medicinal product, the competent authority (assessment organization) of the reference Member State may give a notice in writing and/or in electronic format requesting from the applicant to provide it with the missing additional information necessary to explain or clarify the documents or particulars provided in the marketing authorization application dossier (including proposals on amendments to the SmPC, medication guide, mock-ups of the packaging of the medicinal product, normative document or other documents of the marketing authorization application dossier) using the templates provided in Appendices 6 to 8 to these Rules.

94. Within 90 calendar days beginning with the day the assessment is started, the competent authority (assessment organization) of the reference Member State shall send copies of the reports containing observations and requests using the templates provided in Appendices 6 to 8 to these Rules and the draft assessment report using the template provided in Appendix 11 to these Rules, to the competent authority (assessment organization) of the Member State concerned.

If there are requests sent to the applicant, the competent authority (assessment organization) of the Member State concerned shall send the requests to the competent authority (assessment organization) of the reference Member State within 30 calendar days beginning with the day the draft assessment report of the reference Member State is received. The reference Member State shall prepare a single request within 5 business days beginning with the day the last request from the Member State concerned is received and shall send it to the applicant as laid down in paragraph 93 of these Rules.

The assessment shall be suspended beginning with the day the observations are sent to the applicant. After the first request, the subsequent requests are acceptable only if the information provided by the applicant in response to the previous request causes to raise additional questions.

95. The period to response by the applicant to that request should be a maximum of 90 calendar days. The procedures for sending requests and receiving responses for such requests shall be established in the Member States legislation.

As applicable and subject to the appropriate application, the applicant's response period may be further extended by the competent authority of the reference Member State. The total period for the response to requests should be a maximum of 180 calendar days.

96. The total period for the response by the applicant to requests to the competent authority (assessment organization) within the granting a marketing authorization should be a maximum of 180 calendar days.

The period for providing these documents requested by the competent authority (assessment organization) in the course of assessment of the medicinal product by the applicant is not to be counted in the period of granting a marketing authorization for, and the assessment of, the medicinal product.

97. The assessment shall be resumed upon the competent authority (assessment organization) of the reference Member State is provided with the applicant's response to the assessors' observations.

98. If the applicant does not provide the documents or particulars requested by the competent authority (assessment organization) in due time, the assessment of, and the procedure of granting a marketing authorization for, a medicinal product shall be terminated. The competent authority (assessment organization) shall inform the applicant and competent authorities (assessment organizations) in writing or electronically on that decision within 14 calendar days beginning with the day such a decision is made.

99. If a pharmaceutical inspection to verify compliance with the requirements of the Good Pharmaceutical Practices of the Union is triggered, the assessment of a medicinal product is not to be suspended. In doing so, an assessment report shall be finalized by the reference Member State only when the assessment organization of the reference Member State has received the inspection report. An unscheduled pharmaceutical inspection together with the drawing up a report on such an inspection should be carried out within the period of granting a marketing authorization for a medicinal product and not exceeding a maximum of 180 calendar days beginning the day the

decision on triggering the inspection is made by the competent authority (assessment organization).

The applicant shall arrange a visit to the manufacturing site, trial site, or marketing authorization holder's pharmacovigilance system within 30 calendar days beginning with day the information on the necessity of such an inspection is received or shall propose potential dates of the visit within 90 calendar days after the information on the necessity of such an inspection is received.

100. Communications between competent authorities (assessment organizations) when sending requests to the applicant shall be carried out electronically using the template provided in Appendix 18 to these Rules via the Integrated System.

101. Where a Member State concerned does not send any response in respect of the medicinal product under assessment (observations, evaluation of the draft assessment report), the reference Member State shall acknowledge that that Member State concerned agrees with the opinion (including any observations, as applicable) contained in the draft assessment report.

102. Written communications between competent authorities (assessment organizations) of the reference Member State and Member States concerned shall be implemented electronically via the Integrated System.

103. To draw up an assessment report, the assessment organization of the reference Member State shall draw up assessment reports on the quality aspects, on a new active substance contained in a medicinal product, on the active substance master file, on the non-clinical, clinical aspects, the laboratory testing record (if the assessment organization has performed respective tests) using the templates provided in Appendices 6 to 10, 12, and 22 to these Rules.

Assessment reports on the quality, non-clinical, and clinical aspects, and a final assessment report shall be drawn up as laid down in Appendices 13 to 15 and 23 to these Rules.

A final assessment report of the reference Member State shall be drawn up using the template provided in Appendix 16 to these Rules.

104. Within a maximum of 155 calendar days beginning with the day the application is submitted for the granting a marketing authorization, the competent authority (assessment organization) of the reference Member State shall send the draft assessment report drawn up using the template provided in Appendix 16 to these Rules together with the applicant's responses to the requests, the draft SmPC, draft medication guide (patient leaflet), draft mock-ups of the packaging, draft normative document, and draft Risk Management Plan in the course of use of the product as appropriate to the applicant and the Member States concerned.

Where the assessment organization of the reference Member State draws up a negative draft assessment report and the decision to refuse to grant the marketing authorization is made under paragraph 114 to these Rules, the assessment of, and the procedure of granting a marketing authorization for, a medicinal product shall be terminated. The competent authority (assessment organization) shall notice the applicant electronically and/or in writing on that decision within 14 days beginning with the day such a decision is made, accompanying such a decision with the aforementioned final assessment report.

Where the assessment organization of the reference Member State draws up a positive draft assessment report, the competent authorities (assessment organizations) of the Member States concerned shall evaluate such a report.

105. Where no observations are set forward by the competent authorities (assessment organizations) of the Member States concerned or where such observations are resolved as laid down in paragraph 106 of these Rules, the competent authorities (assessment organizations) of the reference Member States and of the Member States concerned shall finalize the assessment of the medicinal product within 10 business days (by the 175^{th} day beginning with the day an application for granting a marketing authorization is submitted).

106. Where the competent authorities (assessment organizations) of the Member States concerned set forward observations to the draft assessment report, the draft SmPC, draft medication guide, draft mock-ups of the packaging, draft normative document, and draft Risk Management Plan in the course of use of the product as appropriate, the competent authorities (assessment organizations) of the Member States concerned where necessary shall consult electronically with the competent authority (assessment organization) of the reference Member

States or Member States concerned within 10 business days using the template provided in Appendix 18 to these Rules (by the 165th day beginning with the day an application for granting a marketing authorization is submitted).

107. In case disagreement unresolved during the consultation, the competent authority (assessment organization) of the Member State concerned shall send its opinion not approving the assessment report drawn by the assessment organization of reference Member State together with the exposition of the grounds for the negative decision to the competent authority (assessment organization) of the reference Member State and of Member States concerned as well as to the Expert Committee within a maximum of 10 business days beginning with the day the final assessment report of the reference Member State is received and taking into account the provision of paragraphs 106 of these Rules, using among other things paper format.

108. The Expert Committee shall carry out a procedure to resolve disagreement as laid down in the Rules of Procedure subject to approval by the Commission, within a maximum of 60 calendar days beginning with the day the Member States concerned send the opinion not approving the favorable assessment report drawn up by the assessment organization of the reference Member State.

Where disagreement on the assessment report between competent authorities of the reference Member State and of Member States concerned is resolved, they shall finalize the assessment and proceed to the issuing the final documents as laid down in paragraph 105 and 109 to 113 of these Rules.

In case disagreement between the competent authorities of the reference Member State and of Member States concerned as regards of approving the assessment report is not resolved, the competent authorities of the reference Member State and of the Member States concerned which have recognized the assessment report shall finalize the assessment and proceed to issuing the final documents as laid down in paragraph 105 and 109 to 113 of these Rules. On applicant's request, the competent authorities of such Member States concerned may postpone the issuance of the certificate of marketing authorization up until the agreement is reached between the competent authorities of other Member States concerned and of the reference Member State.

109. The competent authorities (assessment organizations) of the reference Member State and of the Member States concerned which have made positive decision on the granting a marketing authorization for a medicinal product based on the outcome of the assessment and as laid down in paragraphs 105 and 108 of these Rules shall proceed to issuing the final documents within a maximum of 30 calendar days. Among other things, within this period and within a maximum of 10 business days the applicant must translate the SmPC, draft medication guide, mock-ups of the packaging into official languages of the Member States where such a requirement is provided by the Member State legislation.

110. Within a maximum of 30 calendar days (by the 205th day beginning with the day an application for the granting a marketing authorization is submitted)—

a) the competent authority of the reference Member State shall issue a certificate of marketing authorization to the applicant using the template provided in Appendix 17 to these Rules, the approved SmPC, medication guide, normative document, mock-ups of the packaging, the assessment report (where necessary the applicant shall be provided with the approved translation of the SmPC, medication guide and mock-ups of the packaging of the medicinal product into the official language of the reference Member State), and the approved Risk Management Plan in the course of use of the product (as appropriate);

b) the competent authorities of the Member States concerned shall issue a certificate of marketing authorization to the applicant using the template provided in Appendix 17 to these Rules, the approved SmPC, medication guide, mock-ups of the packaging drawn up using the official language of the Member State concerned where such a requirement is provided by the Member State concerned legislation, and the approved Risk Management Plan in the course of use of the product (as appropriate).

111. As laid down in the procedure for establishing and maintaining the Common Register, competent authorities of the reference Member State and of the Member States concerned make publicly available the information on the medicinal product and the active substances contained therein in the Common Register together with the approved SmPC, medication guide, mock-ups

of the packaging, normative document, and on the final assessment report drawn up as laid down in Appendix 16 to these Rules excluding the confidential data and data on assessors, on the approved Risk Management Plan in the course of use of the product medicinal product (as appropriate).

112. The competent authority of the Member State concerned shall issue a certificate of marketing authorization for a medicinal product valid within the period as laid down in by the reference Member State.

113. The reference Member State must update the assessment report whenever new information becomes available which is important for the evaluation of the quality, safety or efficacy of the medicinal product concerned.

114. The competent authority of the reference Member State shall refuse to grant a marketing authorization within the decentralized procedure in the following cases:

a) the risk-benefit balance of the medicinal product is not considered to be favorable;

b) its therapeutic efficacy is insufficiently substantiated by the applicant;

c) the quality of the medicinal product has not been demonstrated;

d) the proposed quality control test methods are not verifiable;

e) the applicant has submitted the false information;

f) compliance with the Good Pharmaceutical Practice of the Union has not been demonstrated based on the outcome of the inspection within the procedure of granting a marketing authorization for a medicinal product.

115. The competent authority of the Member State concerned shall not recognize the assessment report drawn up by the assessment organization of the reference Member State and shall, thus, refuse to grant a marketing authorization under the decentralized procedure if based on the outcome of the assessment of the marketing authorization application dossier of a medicinal product and upon completion of the procedure of resolving the disagreement in the Expert Committee the decision is made that the data provided in the assessment report are insufficient to assure the quality, efficacy, and/or positive risk-benefit balance of the medicinal product.

VII. ESTABLISHING OF POST-MARKETING MEASURES (CONDITIONAL MARKETING AUTHORIZATION)

116. The competent authority (assessment organization) of the reference Member State may establish one or more of the following additional requirements in respect of a medicinal product within granting of marketing authorization for that product:

- to take certain measures for ensuring the safe use of the medicinal product to be included in the risk management system;
- to conduct post-authorisation safety studies of the medicinal product;
- to introduce additional obligations on the marketing authorization for the medicinal product or reporting of suspected adverse reactions;
- to conduct post-authorisation efficacy studies and where necessary studies of some aspects of the efficacy of the medicinal product which can be resolved only after the medicinal product has been marketed;
- other conditions or restrictions to ensure safe and efficacious use of the medicinal product in accordance with the requirements of the Good Pharmacovigilance Practice of the Eurasian Economic Union.

The conditions and restrictions imposed and the timeline of implementation thereof shall be included in the certificate of marketing authorization, Common Register, and SmPC and medication guide.

117. The medicinal product which is the subject to the procedures described in this paragraph may remain on the market of the Union only on favorable outcome of the assessment of risk-benefit balance carried out annually by the competent authority (assessment organization) of the reference Member State with drawing up the assessment report on the medicinal product.

The competent authority of the reference Member State may revoke the certificate of marketing authorization for a medicinal product whenever the marketing authorization holder fails to comply with the additional obligations imposed by the competent authority of the reference

Member State in respect of that medicinal product within granting a marketing authorization or other procedures related to authorization as laid down in paragraph 116 of these Rules and where favorable risk-benefit balance is not demonstrated based on the outcome of the annual assessment of the risk-benefit balance carried out by the competent authority (assessment organization) of the reference Member State.

118. The granting or confirmation (renewal) of a marketing authorization may be conditioned by the competent authority on imposing an obligation on the marketing authorization holder:

a) to conduct a post-authorization safety studies if there are concerns about the risks of such a medicinal product. If the same concerns apply to more than one medicinal product, the competent authorities of the Member States shall encourage the marketing authorization holders of such medicinal products to conduct a joint post-authorization safety study;

b) to conduct a post-authorization efficacy study when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly.

119. The marketing authorization holder may present written observations in response to the imposition of the obligation referred to in paragraph 118 of these Rules within a maximum of 90 calendar days beginning with the day the appropriate notice on imposition of an obligation by the competent authority (assessment organization) is received.

120. On the basis of the written observations submitted by the marketing authorization holder under paragraph 118 of these Rules, the competent authority (assessment organization) shall withdraw or confirm the obligation to conduct the studies referred to in paragraph 118 of these Rules, within 30 calendar days. Where the obligation referred to in paragraph 118 of these Rules is confirmed, the marketing authorization shall be varied to include the obligation as a condition of the marketing authorization and the risk management system shall be updated accordingly.

VIII. CONFIRMATION (RENEWAL) OF THE MARKETING AUTHORIZATION FOR A MEDICINAL PRODUCT

121. For all Member States where a medicinal product is authorized for marketing, the date of confirmation (renewal) of the marketing authorization for the medicinal product is determined by the day of granting the marketing authorization for the medicinal product in the reference Member State under the mutual recognition procedure or decentralized procedure.

For medicinal products which have not been designated as orphan medicinal product in any Member State as laid down in the legislation of such a Member State, the date of confirmation (renewal) of the marketing authorization is determined by the day of granting a marketing authorization for that medicinal product in that Member State of the Union under the mutual recognition procedure.

122. The confirmation (renewal) of the marketing authorization shall be carried out on the basis of a re-evaluation of the risk-benefit balance by the competent authority (assessment organization) of the reference Member State and the assessment report on the medicinal product shall be drawn up.

The assessment of the medicinal product in the course of confirmation (renewal) of the marketing authorization in Member States concerned shall be carried out in the form of:

- evaluation of the application, documents and particulars of the marketing authorization application dossier; and

- evaluation of the assessment report drawn up by the reference Member State.

A medicinal product may be marketed on the Union market within the procedure of confirmation (renewal) of a marketing authorization.

123. The applicant shall submit an application for confirmation (renewal) of a marketing authorization to all Member States where the medicinal product is authorized.

124. Where the marketing authorization holder fails to submit an application for the confirmation (renewal) of a marketing authorization before the end of validity of a certificate of

marketing authorization, the certificate of marketing authorization for a medicinal product shall cease to be valid.

125. The confirmation (renewal) of a marketing authorization shall be completed within a maximum of 120 calendar days beginning with the day an application for confirmation (renewal) of a marketing authorization is submitted.

126. The application for confirmation (renewal) of the marketing authorization of the medicinal product may not be submitted earlier than 210 calendar days before the marketing authorization ceases to be valid in the reference Member State but before the day the marketing authorization ceases to be valid.

127. For the confirmation (renewal) of the marketing authorization for a medicinal product, the applicant shall provide the competent authority (assessment organization) of the reference Member State with the following documents and materials:

a) the application for confirmation (renewal) of the marketing authorization for a medicinal product in paper and/or electronic format completed as laid down in Appendix 2 to these Rules;

b) the documents confirming payment of a fee (duty) for confirmation (renewal) of the marketing authorization and the assessment as required by the reference Member State legislation;

c) the Modules 1 and 2 of the marketing authorization application dossier drawn up as laid down in Appendices 1 to 5 to these Rules in electronic format.

128. The competent authority (assessment organization) of the reference Member State should provide an access to the marketing authorization application dossier to the competent authorities (assessment organizations) of the Member State concerned via the Integrated System within 5 business days beginning with the day the applicant submits the documents referred to in paragraph 127 of these Rules.

The competent authorities (assessment organizations) of the Member State concerned shall access the marketing authorization application dossier of the medicinal product using the Integrated System.

129. Having submitted the application for confirmation (renewal) of the marketing authorization to the competent authority (assessment organization) of the reference Member State, the applicant shall submit following items to the competent authorities (assessment organizations) of the Member States within 14 business days:

a) the application in paper and/or electronic format completed as laid down in Appendix 2 to these Rules;

b) the documents confirming payment of a fee (duty) for the confirmation (renewal) of the marketing authorization and the assessment as laid down in the Member State concerned legislation;

c) the Module 1 of the marketing authorization application dossier in electronic format; and

d) if the respective requirements exist in the Member State legislation, the SmPC, medication guide, and mock-ups of the packaging of the medicinal product are also to be submitted in the official language of the Member State concerned.

130. The competent authority (assessment organization) of the reference Member State shall verify the completeness and accuracy of format of the documents submitted in the marketing authorization application dossier within 14 days beginning with the day the application for confirmation (renewal) of the marketing authorization is submitted, before the assessment of the marketing authorization application dossier is started. The applicant is given a maximum of 90 calendar days which are not to be counted in the period of renewal and assessment of a medicinal product to provide missing materials to be included in the marketing authorization application dossier in response to the observations of the competent authority (assessment organization) of the reference Member State.

131. The competent authority (assessment organization) of the reference Member State shall refuse to accept an application for confirmation (renewal) of the marketing authorization for a medicinal product in case of failure to submit the marketing authorization application dossier materials in response to the observations and/or payment of a fee (duty) for the confirmation (renewal) of the marketing authorization for a medicinal product and for the assessment thereof, as required by the reference Member State legislation, is not confirmed, or due failure to submit the application for confirmation (renewal) of the marketing authorization within timeline referred

to in paragraph 126 of these Rules, and shall notify electronically the applicant and the competent authorities (assessment organizations) of the Member States concerned.

132. Within 50 calendar days beginning with the day the application for confirmation (renewal) of the marketing authorization for a medicinal product is submitted to the competent authorities (assessment organization) of the Member State concerned, the competent authority (assessment organization) of the reference Member State in the course of assessment of the medicinal product shall draw up and send the draft assessment report using the template provided in Appendix 11 to these Rules, to the competent authority (assessment organization) of the Member State concerned using the Integrated System.

133. In case of disagreement with the opinion provided in the draft assessment report of the reference Member State as regards of the risk-benefit balance of a medicinal product or where the competent authorities (assessment organizations) of the Member States concerned require to amend the SmPC, medication guide, mock-ups of the packaging or other documents of the marketing authorization application dossier, the competent authority (assessment organization) of the Member State concerned shall send an appropriate request to the competent authority (assessment organization) of the reference Member State within a maximum of 20 calendar days beginning with the day the competent authority (assessment organization) of the reference Member State sends the draft assessment report, using the Integrated system.

134. When the Member States concerned evaluate the draft assessment report drawn up by the assessment organization of the reference Member State, when the competent authorities (assessment organizations) of the reference Member State evaluate requests sent by the competent authorities (assessment organizations) of the Member States concerned, and when the competent authorities (assessment organizations) of the Member States concerned evaluate the final assessment report drawn up by the assessment organization of the reference Member State, the competent authorities (assessment organizations) of the Member States participating in the procedure shall communicate to each other via the Integrated System and using the template provided in Appendix 18 to these Rules; in the course of such communications agreement shall be reach on the final assessment report drawn up by the assessment organization of the reference Member State.

135. During the procedure of confirmation (renewal) of the marketing authorization for, and/or assessment of, a medicinal product, the competent authority (assessment organization) of the reference Member State may give a notice in writing and/or electronically requesting from the applicant to provide it with missing additional information necessary to explain or clarify the documents or particulars provided in the marketing authorization application dossier (including proposals on amendments to the SmPC, medication guide, mock-ups of the packaging of the medicinal product, normative document or other documents of the marketing authorization application dossier).

The applicant should provide a response to the aforementioned request within a maximum of 90 calendar days. The period for providing the documents requested by the competent authority (assessment organization) of the reference Member State by the applicant in the course of confirmation (renewal) of a marketing authorization for, and assessment of, a medicinal product is not to be counted in the period of the procedure of confirmation (renewal) of the marketing authorization for, and assessment of, the medicinal product.

The competent authority (assessment organization) of the reference Member State shall consider the applicant’s responses, including those of the competent authorities’ (assessment organizations’) of the Member States concerned within a maximum of 20 calendar days in the course of the assessment of the medicinal product.

If the applicant does not provide the requested documents or particulars in due time, the assessment of, and the procedure of confirmation (renewal) of the marketing authorization for, a medicinal product shall be terminated. The competent authority (assessment organization) of the reference Member State shall inform the competent authorities (assessment organizations) of the Member States concerned and applicant in writing or electronically on that decision within 14 calendar days beginning with the day such a decision is made.

136. Based on the outcome of the assessment of a medicinal product and within a maximum of 90 calendar days beginning with the day the application for confirmation (renewal) of the

marketing authorization for the medicinal product is submitted, the competent authority (assessment organization) of the reference Member State shall draw up and approve a final assessment report using the template provided in the Appendix 16 to these Rules and shall send it to the competent authorities (assessment organizations) of the Member States concerned participating in the confirmation (renewal) of the marketing authorization for the medicinal product, using the Integrated System. The assessment report shall be drawn up as laid down in Appendices 13 to 15 and 23 to these Rules.

137. The competent authority (assessment organization) of the Member State concerned based on the outcome of the assessment of a medicinal product and within a maximum of 20 calendar days beginning with the day it receives the final assessment report drawn up by the reference Member State shall draw up, approve and send its opinion on approvability of the assessment report drawn up by the reference Member State to the competent authority (assessment organization) of the reference Member State, using the template provided in Appendix 18 to these Rules and using the Integrated System.

138. The proposals of the competent authorities (assessment organizations) of the reference Member State and of the Member States concerned on the amendment to the SmPC, medication guide, mock-ups of the packaging of the finished product or other documents of the marketing authorization application dossier may not substantiate the refusal of the confirmation (renewal) of the marketing authorization for the medicinal product should the applicant agree with such an amendment.

139. Where, based on the outcome of the assessment of a medicinal product, the reference Member State establishes the favorable risk-benefit balance and compliance of the marketing authorization application dossier with the requirements:

a) the competent authority of the reference Member State shall issue a certificate of marketing authorization of unlimited validity to the applicant using the template provided in Appendix 17 to these Rules, the approved SmPC, medication guide, normative document, mock-ups of the packaging, the assessment report (where necessary the applicant shall be provided with the approved translation of the SmPC, medication guide and mock-ups of the packaging of the medicinal product into the official language of the reference Member State), and the approved Risk Management Plan in the course of use of the product (as appropriate);

b) the competent authorities of the Member States concerned shall issue a certificate of marketing authorization of unlimited validity to the applicant using the template provided in Appendix 17 to these Rules, the approved SmPC, medication guide, mock-ups of the packaging drawn up using the official language of the Member State concerned where such a requirement is provided by the Member State concerned legislation; and

c) The competent authorities of the Member State participating in the confirmation (renewal) of the marketing authorization shall make publicly available the necessary information on the medicinal product and the active substances contained therein in the Common Register together with the approved Risk Management Plan in the course of use of the product medicinal product (as appropriate).

140. If the assessment report drawn up by the assessment organization of the reference Member State cannot be recognized, the competent authority (assessment organization) of the Member State concerned shall send its opinion not approving that assessment report to the competent authorities (assessment organizations) of the reference Member State and of other Member States concerned participation in the procedure of confirmation (renewal) of the marketing authorization for a medicinal product, to the applicant, and Expert Committee within the period referred to in paragraph 137 of these Rules, together with the grounds for such a decision using electronic and/or paper format.

141. The Expert Committee shall carry out a procedure to consider the disagreement as laid down in the Rules of Procedure subject to approval by the Commission, within a maximum of 60 calendar days beginning with the day the opinion not approving the assessment report drawn up by the assessment organization of the reference Member State is received.

The competent authority of the Member State concerned shall refuse to confirm the marketing authorization (renew the marketing authorization) for a medicinal product if based on the outcome of the assessment of the medicinal product and upon completion of the procedure of

resolving the disagreement in the Expert Committee it is concluded that the assessment report drawn up by the assessment organization of the reference Member State cannot be recognized by the competent authority (assessment organization) of the Member State concerned due to grounds referred to in paragraph 146 of these Rules.

142. In the course of confirmation (renewal) of the marketing authorization for a medicinal product, the competent authority (assessment organization) of the Member State shall verify whether the marketing authorization holder complies with the conditions of the granting a marketing authorization for a medicinal product referred to in section VII of these Rules if those obligations were imposed on that marketing authorization holder. If new safety or efficacy data of medicinal product becomes available, the competent authority may vary the conditions of granting the marketing authorization and/or impose new conditions.

In the course of evaluation of marketing authorization application dossier within the confirmation (renewal) of the marketing authorization for a medicinal product, the competent authorities (assessment organizations) of the Member States shall verify whether the marketing authorization holder complies with the obligation to keep the product information up to date with the current scientific knowledge including the conclusions of the assessment and recommendations of the competent authority (assessment organization).

143. Where in the course of the assessment of a medicinal product or the confirmation (renewal) of a marketing authorization the competent authority (assessment organization) of the reference Member State finds that the obligations referred to in paragraph 142 of these Rules are not complied with due to the objective reasons and the variation to the marketing authorization for a product application dossier is necessary, the normative document, SmPC, medication guide, and Risk Management Plan as appropriate needs to be updated by the marketing authorization holder who shall trigger the variation to the marketing authorization application dossier within a maximum of 180 calendar days beginning with the day the competent authority (assessment organization) of the reference Member State sends a request to vary the marketing authorization application dossier, after the reference Member State makes the favorable opinion on confirmation (renewal) of a marketing authorization for the medicinal product.

144. The competent authority (assessment organization) of the reference Member State may accept the type I variation to the marketing authorization application dossier for a medicinal product as laid down in Appendix 19 to these Rules in the course of the confirmation of a marketing authorization (renewal of the marketing authorization) for a medicinal product to avoid additional submission of the application for variation to the marketing authorization application dossier.

145. On the grounds relating to pharmacovigilance and taking into account circumstances referred to in paragraphs 143 and 144 of these Rules, in the course of the confirmation of a marketing authorization (renewal of the marketing authorization) for a medicinal product, the competent authority of the reference Member State based on the outcome of the assessment of the medicinal product may decide to proceed with a five-year certificate of marketing authorization which is subject to renewal at the end of this five-year period of validity.

146. The competent authority of the reference Member State may refuse to confirm a marketing authorization (renewal a marketing authorization) or the competent authority of the Member State concerned may refuse to recognize the assessment report on the following grounds:

a) the following serious risks of the medicinal product are remaining at the moment of confirmation (renewal) of a marketing authorization:

the risk-benefit balance proves to be unfavorable or the therapeutic efficacy proves to be lacking when the medicinal product is used according to the SmPC;

the pharmacovigilance data indicates that the risk-benefit balance is unfavorable, including significant increase of the rate of reporting of any adverse reactions in comparison with information included in the approved SmPC;

the qualitative and quantitative composition is not as declared or in case of repeated quality defects of the medicinal product in the course of its marketing in the Union;

false or obsolete information in the marketing authorization application dossier accompanying the application for the confirmation (renewal) of the marketing authorization;

b) the marketing authorization holder fails to resolve the observations or to provide answers on questions raised in the course of the assessment of the medicinal product in the timely manner;

c) the marketing authorization holder fails to comply with the pharmacovigilance obligations or obligations of the conditional marketing authorization.

IX. VARIATION TO THE MARKETING AUTHORIZATION APPLICATION DOSSIER FOR A MEDICINAL PRODUCT

147. After a marketing authorization has been granted, the marketing authorization holder shall introduce any changes (hereinafter referred to as variations) that may be required to enable the medicinal product to be manufactured and checked by means of generally accepted scientific methods.

Those changes shall be subject to the approval of the competent authority of the Member State where the medicinal product has been granted the marketing authorization (or that competent authority shall be notified in accordance with the appropriate procedure). In doing so, the applicant shall trigger the variation the marketing authorization for the medicinal product via the competent authority (assessment organization) of the same reference Member State which has granted the marketing authorization for the medicinal product.

148. The marketing authorization holder shall provide the competent authority of the Member State with any new information which might entail the amendment of the particulars or documents of the marketing authorization application dossier of a medicinal product.

The marketing authorization holder shall forthwith inform the competent authority of the Member State of any prohibition or restriction imposed by the competent authorities of any country in which the medicinal product is marketed and of any other new information which might influence the evaluation of the risk-benefit balance of the medicinal product concerned. The information shall include both positive and negative results of clinical trials or other studies in all indications and populations, whether or not included in the marketing authorization, as well as data on the use of the medicinal product where such use is outside the terms of the marketing authorization.

149. The marketing authorization holder shall ensure that the product information is kept up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations of medicines competent authorities of other countries.

150. In order to be able to continuously assess the risk-benefit balance of the authorized medicinal product, the competent authority (on its own or on the request of the assessment organization) may ask the marketing authorization holder to forward data demonstrating that the risk-benefit balance of the authorized medicinal product remains favorable. The marketing authorization holder shall provide that competent authority (assessment organization) with the necessary particulars as soon as possible but not later than 30 calendar days beginning with the day the appropriate request is received.

The competent authority (on its own or on the request of the assessment organization) may at any time ask the marketing authorization holder to submit a copy of the pharmacovigilance system master file. The marketing authorization holder shall submit the copy at the latest 10 business days after receipt of the request.

151. Variations to the marketing authorization shall not have negative unfavorable impact on the risk-benefit balance of the authorized medicinal product.

152. Variations to the marketing authorization shall be introduced in accordance with the classification of variations to the marketing authorization and Rules concerning the introduction of variations as laid down in Appendices 19 and 20 to these Rules. The assessment of variations to the marketing authorization shall be carried out with Appendix 20 to these Rules. The assessment report on the variations to the marketing authorization shall be drawn up based on the outcome of that assessment as laid down in Appendix 21 to these Rules.

153. In case of a favorable decision of the competent authority (assessment organization) of the Member State on the variation to a marketing authorization and where the variation concerns with the information and particulars outlined in a certificate of marketing authorization, a new certificate of marketing authorization shall be issued to the applicant using the same certificate

number and it shall be valid for remaining period of validity of the marketing authorization. A record shall be made in the Common Register describing each variation together with its details and the dossier section which is the subject of the variation.

154. Where a need for the variation to a marketing authorization emerges within the last 90 days of validity of the marketing authorization, the variation may be allowed in the course of assessment of a medicinal product within the procedure of confirmation (renewal) of the marketing authorization.

155. For variations to a marketing authorization in the mutual recognition procedure, the applicant shall communicate to the competent authority (assessment organization) of the reference Member State the list of dispatch dates of appropriate applications for the variations to the marketing authorization have been sent to Member States concerned and confirmation that the fees (duties) for variation to the marketing authorization (and the assessment of a medicinal product as appropriate) have been paid as required by the Member State concerned legislation, together with the variation procedure numbers as laid down in Appendix 19 to these Rules which have been carried out in the Member States concerned.

In case of transfer of a marketing authorization in all or some (one) Member States where the medicinal product has been authorized, the applicant shall submit an application for a variation as laid down in Appendix 2 to these Rules and appropriate documents of the Module 1 of the marketing authorization application dossier to the competent authority (assessment organization) of that Member States.

156. Within the assessment period of a variation to a marketing authorization for a medicinal product, the assessment organization and competent authority of the reference Member State may give a notice in writing and/or electronically requesting from the applicant to provide it with missing additional information necessary to explain or clarify the documents or particulars provided in the application dossier (including proposals on amendments to the SmPC, medication guide, mock-ups of the packaging of the medicinal product, normative document or other documents of the marketing authorization application dossier). After the first request, the subsequent requests are acceptable only if the information provided by the applicant in response to the previous request causes to raise additional questions. The period to response by the applicant to the that request shall be a maximum of 90 calendar days. The period for response to the request of the competent authority or assessment organization within the procedure of variation to the marketing authorization or assessment thereof is not to be counted in the period of variation to the marketing authorization or assessment thereof. The competent authority (assessment organization) shall inform the applicant in writing or electronically on that decision within 14 calendar days beginning with the day such a decision is made.

157. Where variation to the medication guide for a medicinal product is made, competent authority shall approve a new medication guide for the medicinal product and provide the applicant with it.

158. In case of confirmation (renewal) of a marketing authorization for a medicinal product or where following variations to the marketing authorization A.1, A.4, A.5, A.6, A.7, B.II.b.1, B.II.b.4, as well as bar code or color design of the packaging or other type IA or type IB variations which do not significantly impact on the safety, quality, or efficacy of the medicinal product, but which may influence the mock-ups of the packaging of the medicinal product, SmPC and/or medication guide are made, the manufacturing or importation of the medicinal product shall be allowed using the authorized packaging and medication guide within 180 calendar days beginning with the day the marketing authorization is confirmed (renewed) or varied in accordance with the information included in the marketing authorization application dossier and up until the day the marketing authorization is confirmed (renewed) or varied. The distribution of a medicinal product is allowed in the amended and not amended packaging and using the amended and not amended medication guide up until the product is expired where such distribution does not violate with the requirements of Rules of the Good Pharmacovigilance Practice subject to the approval by the Commission.

X. SUSPENSION, WITHDRAWAL (REVOCATION) OF A CERTIFICATE OF MARKETING AUTHORIZATION FOR A MEDICINAL PRODUCT OR RESTRICTIONS ON USE OR VARIATION TO THE CONDITIONS OF A MARKETING AUTHORIZATION

159. Member States shall suspend the marketing authorization or restrict the supply of the medicinal product, if the view is taken that:

- there is a documented evidence that qualitative and quantitative composition of released batches of the medicinal product is not as declared;
- the medicinal product is hazardous (it causes serious and irreversible harm to human health (the competent authority (assessment organization) shall draw up an assessment report in support of the serious and irreversible harm to human health together with the reference documents));
- the unfavorable risk-benefit balance is shown or the lack of therapeutic efficacy of the medicinal product when used in accordance with the SmPC conditions is established;
- the favorable risk-benefit balance is not shown within the reassessment of the risk-benefit balance carried out annually by the competent authority (assessment organization) as laid down in paragraph 117 of these Rules;
- there are false documents or particulars in the marketing authorization application dossier;
- the manufacturer has not resolved incompliance of the methods of manufacture and control described in the marketing authorization application dossier discovered by the inspection within the time limits set by the competent authority (assessment organization);
- the marketing authorization holder has not fulfilled the pharmacovigilance obligations; or
- the marketing authorization holder has not fulfilled the obligations imposed by the competent authority (assessment organization) as laid down in the paragraphs 116 and 118 of these Rules.

Where the marketing authorization has been suspended under subparagraph 2, 3 or 4 of the paragraph above, the competent authority shall request from the marketing authorization holder to vary the appropriate documents of the marketing authorization application dossier within the time limits it considers appropriate.

160. The competent authority (assessment organization) shall make a decision to withdraw (revoke) the marketing authorization for a medicinal product and to exclude the medicinal product from the Common Register in the following cases:

a) the marketing authorization holder or its legal representative has submitted an application to withdraw the marketing authorization for the medicinal product;

b) the marketing authorization holder has failed to comply with the requirements of the competent authority (assessment organization) referred to in subparagraphs 1 and 2 of paragraph 159 of these Rules;

c) competent authority (assessment organization) has concluded that the marketing authorization holder failed to resolve incompliance of the methods of manufacture and control described in the marketing authorization application dossier discovered by the inspection within the established time limits.

161. Where paragraph 159 or 160 of these Rules apply, competent authorities of the Member States shall take all appropriate measures to ensure that the supply of the medicinal product is prohibited and the medicinal product withdrawn from the market.

162. The competent authority may, for a medicinal product for which the supply has been prohibited or which has been withdrawn from the market, in exceptional circumstances during a limited period allow the supply of the medicinal product to patients having life-threating conditions who are already being treated with the medicinal product.

XI. THE MARKETING CONDITIONS OF MEDICINAL PRODUCTS IN THE MEMBER STATES

163. Medicinal products authorized as laid down in these Rules and included in the Common Register shall be marketed within the Member States they have been authorized in.

164. Medicinal products authorized in the Member States and not brought into compliance with the requirements of the Union before 31 December 2025 shall be marketed within that Member State up until the expiration date.

165. Where the marketing authorization of a medicinal product ceased to be valid, distribution of such a product in the Member States shall be allowed within the expiry period if they have been manufactured within the period of validity of the marketing authorization.

XII. OBLIGATIONS OF THE MARKETING AUTHORIZATION HOLDERS

166. The marketing authorization holder shall promptly provide the comprehensive information on request from a competent authority of any Member State where the medicinal product has been authorized.

167. The marketing authorization holder shall be obliged to notify the competent authorities of the Member States of its desire to halt manufacturing or distribution of the medicinal product in the Union market within a minimum of 60 days beginning with the day the manufacturing or distribution is halted.

168. In case of transfer of a marketing authorization in the reference Member State or Member States concerned, the new marketing authorization holder shall provide written evidence of such a transfer together with the demonstration its capability to communicate with the marketing authorization holders in other Member States to ensure appropriate compliance with any obligations imposed on that marketing authorization holder.

169. Where the marketing authorization is valid for an unlimited period, the periodic assessment of the risk-benefit balance shall take place based on pharmacovigilance data.

XIII. PROCEDURE FOR BRINGING THE MARKETING AUTHORIZATION APPLICATION DOSSIER FOR A MEDICINAL PRODUCT AUTHORIZED BEFORE THE AGREEMENT ON COMMON PRINCIPLES AND RULES GOVERNING MEDICINAL PRODUCTS WITHIN THE UNION OF 23 DECEMBER 2014 CAME INTO EFFECT OR UP UNTIL 31 DECEMBER 2020, INTO COMPLIANCE WITH THE REQUIREMENTS OF THE UNION

170. Marketing authorization application dossier for medicinal products authorized in the Member States before the Agreement came into effect or using national procedures before 31 December 2020 shall be brought into compliance with the requirements of the Union at the latest on 31 December 2025 in accordance with this procedure.

171. Bringing the marketing authorization application dossier into compliance with the requirements of the Union shall entail submission of a marketing authorization application dossier using the Common Technical Document format as laid down in Appendix 1 to these Rules.

In the course of triggering the procedure of bringing into compliance with the requirements of the Union, the applicant shall submit written confirmation that documents and particulars of the marketing authorization application dossier in the Common Technical Document format are identical in their content to the marketing authorization application dossier and do not contain any changes which impact the quality, efficacy, safety or risk-benefit balance of the medicinal product.

172. Within bringing into compliance with the requirements of the Union, the applicant may in parallel vary the marketing authorization for a medicinal document. In that event, the variation procedure and assessment of a dossier for compliance with the law of the Union to be carried out as laid down in Appendices 19 and 20 to these Rules.

173. Bringing the marketing authorization application dossier for a medicinal product into compliance with the law of the Union shall be completed within a maximum of 100 calendar days beginning with the day of submission of an appropriate application for bringing the marketing authorization application dossier in compliance with the law of the Union.

174. Where a medicinal product had been authorized in more than one Member State before the Agreement came into effect or using national procedures before 31 December 2020, the

applicant shall choose one of them as a reference Member State and submit an application, documents and particulars of the marketing authorization application dossier to the competent authority of that Member State in accordance with paragraph 175 of these Rules. Where the favorable decision is made as regards of bringing the marketing authorization in compliance with the law of the Union, the competent authority (assessment organization) of the reference Member State shall carry out bringing the marketing authorization in compliance in Member States concerned under the mutual recognition procedure as laid down in provisions of paragraphs 66 to 82 of these Rules.

175. For the purposes of bringing the marketing authorization application dossier in compliance with the requirements of the Union and continuing the marketing of a medicinal product within a Member State where it has been authorized for marketing, the applicant shall submit to the competent authority (assessment organization) of the reference Member State where the it has been authorized for marketing the following items:

- the application in paper and/or electronic format completed as laid down in Appendix 2 to these Rules;

- the documents confirming payment of a fee (duty) for bringing in compliance with the requirements of the Union as required by the reference Member State legislation;

- Modules 1 to 3 of the marketing authorization application dossier in electronic format drawn up as laid down in Appendices 1 to 5 to these Rules and Module 1 in paper format if the medicinal product is to be marketed within a Member State where it has been authorized.

All available data on non-clinical and clinical studies performed before the Agreement came into effect as laid down in paragraph 36 of these Rules shall be submitted in this case in Modules 4 and 5 of the marketing authorization application dossier in the form of appropriate reports without mandatory bringing them into compliance with the requirements of the Union.

176. The competent authority (assessment organization) of the reference Member State shall verify the completeness and accuracy of the format of the documents submitted in the marketing authorization application dossier within 14 days before the assessment of the marketing authorization application dossier is started. The applicant is given a maximum of 90 calendar days which are not to be counted in the medicinal product assessment period to provide missing materials to be included in the marketing authorization application dossier in response to the observations of the competent authority (assessment organization) of the reference Member State.

The competent authority (assessment organization) of the reference Member State shall refuse to accept an application for bringing a marketing authorization for a medicinal product into compliance with the requirements of the Union in case of failure to submit missing marketing authorization application dossier materials in response to the observations of the competent authority (assessment organization) of the reference Member State and/or payment of a fee (duty) for bringing a marketing authorization for a medicinal product into compliance with the requirements of the Union, as required by the reference Member State legislation, is not confirmed.

177. Within the procedure of bringing a marketing authorization for a medicinal product into compliance with the requirements of the Union, the competent authority (assessment organization) of the reference Member State may give a notice in writing and/or in electronic format requesting from the applicant to provide it with missing additional information necessary to explain or clarify the documents or particulars provided in the marketing authorization application dossier (including proposals on amendments to the SmPC, medication guide, mock-ups of the packaging of the medicinal product, normative document or other documents of the marketing authorization application dossier).

The period to response by the applicant to that request should be a maximum of 90 calendar days. The period for providing these documents requested by the competent authority or assessment organization in the course of assessment of the medicinal product by the applicant is not to be counted in the period of bringing a marketing authorization for a medicinal product into compliance with the requirements of the Union.

If the applicant does not provide the requested documents or particulars in due time, the assessment and bringing a marketing authorization application dossier for a medicinal product into compliance with the requirements of the Union, shall be terminated. The competent authority

(assessment organization) of the reference Member States shall inform the applicant and competent authorities (assessment organizations) of the Member States concerned as appropriate in writing or electronically on that decision within 14 calendar days beginning with the day such a decision is made.

178. Based on the outcome of assessment of a marketing authorization application dossier, the competent authority (assessment organization) of the reference Member State shall draw up and approve an assessment report taking into account the evaluation of explanations, documents, and information submitted by the applicant in response to the request of the assessment organization or competent authority using the template provided in Appendix 16 to these Rules.

In the course of assessment of a marketing authorization application dossier for a medicinal product within the bringing a marketing authorization for a medicinal product into compliance with the requirements of the Union, reevaluation of the risk-benefit balance shall not be carried out unless paragraph 181 of these Rules apply.

179. The competent authority of the reference Member State shall refuse to bring a marketing authorization for a medicinal product into compliance with the requirements of the Union where, based on the outcome of the assessment, the quality of the medicinal product has not been demonstrated or the risk-benefit balance is not considered to be favorable as laid down in paragraph 178 of these Rules.

180. If the competent authority of the reference Member State has made a positive decision on bringing a marketing authorization application dossier for a medicinal product into compliance with the requirements of the Union based on the outcome of the assessment of the medicinal product, the competent authorities of the Member States where that medicinal product has been authorized and where an application for a bringing a marketing authorization application dossier for a medicinal product into compliance with the requirements of the Union has been submitted shall issue a certificate of marketing authorization to the applicant using the template provided in Appendix 17 to these Rules, the approved SmPC, medication guide, normative document, mock-ups of the packaging, the assessment report (where necessary the applicant shall be provided with the assessment report and approved translation of the SmPC, medication guide and mock-ups of the packaging of the medicinal product into the official language of the reference Member State), the approved Risk Management Plan in the course of use of the product (as appropriate) and shall enter the information on the marketing authorization for the medicinal product in the Common Register.

The competent authorities of the Member States based on the outcome of bringing into compliance with the requirements of the Union shall grant a marketing authorization for an unlimited period where the medicinal product has been authorized in 3 Member States for at least 5 years. Where the medicinal product has been authorized in 3 Member States for less than 5 years, the competent authority of the reference Member State based on the outcome of bringing into compliance with the requirements of the Union shall grant the marketing authorization valid for the next 5 years subject to confirmation (renewal) of the marketing authorization after in the end of that period. In that case, competent authorities of the Member States concerned where an application for bringing into compliance with the requirements of the Union has been submitted shall grant the marketing authorization valid within the period established by the reference Member State.

181. Medicinal products might be applied for a marketing authorization under the mutual recognition procedure in Member States where the medicinal product had not been authorized before the Agreement came into effect or before 31 December 2020 after the marketing authorization application dossier has been brought into compliance with the requirements of the Union.

182. Within bringing into compliance with the requirements of the Union with a view of marketing authorization under the mutual recognition procedure where the medicinal product concerned had not been authorized before the Agreement came into effect or before 31 December 2020, the applicant shall submit following items to the competent authority (assessment organization) of the reference Member State:

- the application in paper and/or electronic format completed as laid down in Appendix 2 to these Rules;

- documents confirming payment of a fee (duty) for granting a marketing authorization for, and the assessment of, a medicinal product as required by the reference Member State legislation; and

- Modules 1 to 5 of the marketing authorization application dossier drawn up as laid down in Appendices 1 to 5 to these Rules if marketing authorization shall be continued under the mutual recognition procedure in Member States where the medicinal product had not been authorized before the Agreement came into effect or before 31 December 2020.

In that event, all available data on non-clinical and clinical studies performed before the Agreement came into effect shall be submitted as laid down in these Rules within Modules 4 and 5 of the marketing authorization application dossier in the form of appropriate reports without mandatory bringing them into compliance with the requirements for drawing up reports on non-clinical tests and clinical studies (trials) provided in the Rules of the Good Laboratory Practice and Rules of the Good Clinical Practice as well as Rules of Performing Bioequivalence Studies of Medicinal Products within the Union subject to approval by the Commission. The Member State where the marketing authorization application dossier has been submitted for bringing into compliance with the requirements of the Union shall act as a reference Member State.

183. Where an assessment report needs be drawn up for purposes of mutual recognition procedure in the Member State where the medicinal product concerned had not been authorized for marketing before the Agreement came into effect or before 31 December 2020, the reevaluation of risk-benefit balance and assessment of the medicinal product shall be carried out as laid down in the provisions of Section V of these Rules.

XIV. TRANSITIONAL PROVISIONS

184. Granting a marketing authorization, confirmation (renewal) of the marketing authorization and variation to the marketing authorization of medicinal products applied for granting a marketing authorization, confirmation (renewal) of the marketing authorization and variation to the marketing authorization before 1 January 2016 shall be carried out as laid down in the Member States legislation. Upon applicant's request, granting a marketing authorization for a medicinal product applied before 31 December 2020 may be carried out as laid down in the Member States legislation and not as laid down in these Rules. Medicinal products authorized in accordance with this paragraph shall be brought into compliance with the requirements of the Union up until 31 December 2025.

185. Confirmation (renewal) of the marketing authorization for medicinal products authorized in Member States before the Agreement came into effect and which have not been subject to bringing into compliance with the requirements of the Union shall be carried out as laid down in the Member States legislation up until 31 December 2025.

186. Distribution of medicinal products in parallel using the previously and newly approved packaging and medication guide within their expiration periods.

Distribution of medicinal products released for marketing within Member States before the marketing authorization application dossier has been brought in compliance with the requirements of the Union shall be allowed within their expiration periods.

XV. SPECIFIC PROVISIONS

187. Where the presentation of a medicinal product contains medical device components, the marketing authorization application dossier shall contain information on those components. In addition, where a medical device of complex nature or it is a complex delivery system, the marketing authorization application dossier shall contain an assessment report on the safety, quality, and efficacy of that medical device from the perspective of its impact on clinical characteristics of a medicinal product as whole.

188. Amendments to the vaccine master file in case of changes in the strain composition of influenza vaccines, as well as marketing authorisation of pandemic and pre-pandemic influenza vaccines and amendments to their master file are made in accordance with Appendix No. 24 to the Rules.
(clause 188 was introduced by Decision of the Council of the Eurasian Economic Commission No. 55 dated 14.06.2018)

Round seal: The Eurasian Economic Commission

APPENDIX 1
to the Rules of authorization and
assessment of medicinal products
for human use

REQUIREMENTS
for a marketing authorization application dossier
(in the Common Technical Document format)

I. GENERAL REQUIREMENTS FOR MODULES OF A DOSSIER ACCOMPANYING AN APPLICATION FOR A MARKETING AUTHORIZATION FOR A MEDICINAL PRODUCT

1. Requirements for Module 1 of a marketing authorization application dossier: Administrative Information

1.0. Cover letter (as in Common Technical Document (hereinafter referred to as CTD))

A cover letter shall be included in this section.

Where necessary, a "Notes to Reviewers" document could be provided as an Appendix to the cover letter, providing further information in order to facilitate navigation (e.g. on hyperlinking, volumes presentation etc …).

1.1. Table of Contents

A comprehensive table of contents of Modules 1 to 5 shall be provided.

1.2. General documentation

1.2.1. Application for marketing authorization for a medicinal product (as paper and electronic submission using *.doc, *.docx и *.pdf formats) completed in accordance with Appendix 2 to these Rules.

1.2.2. Documents confirming the payment of a fee (duty) the assessment of, and for the granting a marketing authorization for, a medicinal product in accordance with the legislation of Eurasian Economic Union Member State (hereinafter referred to as Member States) which is to grant a marketing authorization (unless the Member State legislation prohibits requesting documents which are in possession of or might be retrieved by a Member State independently, from an applicant);

1.2.3. A copy of the Certificate of Pharmaceutical Product complying with the WHO recommendations (properly certified) and issued by the competent authority of the manufacturer's own country (where available).

In the absence of such a certificate, the document (properly certified) that confirms a marketing authorization of a medicinal product in the manufacturer's own country and/or in the marketing authorization holder's own country where appropriate (where available).

Where a marketing authorization of a medicinal product in the manufacturer's own country and/or in the marketing authorization holder's own country has not been granted, an explanation note shall be provided justifying the absence of such data.

1.2.4 Translated into Russian and properly certified copy of the competent authority's assessment report on a marketing authorization in the manufacturer's own country or marketing authorization holder's own country (where available).

1.2.5. A conclusion (recommendation) of the competent authority (assessment organization) of the Member State drawn up based on the outcome of the preliminary scientific advice on the medicinal product in the Member State(s) (where available).

1.2.6. The recommendation of the Expert Committee for Medicinal Products at the Eurasian Economic Commission (hereinafter referred to in as Commission) drawn up based on the outcome of the preliminary scientific advice on the medicinal product (where available).

1.3. Summary of Product Characteristics (hereinafter referred to in as SmPC), medication guide (Patient Leaflet) (hereinafter referred to in as PL), labelling

1.3.1. Draft SmPC, PL drawn up in Russian in accordance with the Requirements for Medication Guide and Summary of Product Characteristics of medicinal products for human use subject to approval by the Commission.

1.3.2. Mock-ups (copies of the flat artwork design in full colour, providing a replication of both the outer and immediate packaging, providing a two-dimensional presentation of the packaging/labelling of the medicinal product. It is generally referred to as a "paper copy" or "computer generated version".) of the outer (user), immediate (inner), and intermediate packaging drawn up in Russian in accordance with the Requirements for Labelling of medicinal products for human use and veterinary medicinal products subject to approval by the Commission. Mock-ups of the intermediate packaging, stickers shall be provided where available.

1.3.3. Consultation with Target Patient Groups on the wording of PL (where available)

When presenting the results of Consultation with Target Patient Groups, the summary of the method of consultation and procedure of drawing up the final version of PL shall be provided. The summary shall be included in this section of the Module in the following form:

- a brief description of the medicinal product;
- consultation or test details, such as method used, explanation on the choice of population consulted, language tested;
- questionnaires used (including instructions and observation forms);
- original and revised PLs;
- summary and discussion of results (subjects' answers, problems identified and revisions made to relevant package leaflet section);
- Conclusion.

All other details should be available on request of the competent authority (assessment organization).

1.3.4. Copies of SPC and PL approved by the competent authority of the manufacturer's own country and/or marketing authorization holder's own country together with the latest revision date certified by the marketing authorization holder (where available).

1.4. Information on regulatory status of a medicinal product in other countries

1.4.1. The list of countries where the medicinal product has been applied for granting a marketing authorization, authorized for marketing, where granting of a marketing authorization has been refused or suspended together with the number and the date of marketing authorization, the period of its validity or the date of decision to refuse granting of a marketing authorization, to suspend a marketing authorization. The information provided shall be certified by the marketing authorization holder.

1.5. Quality documents

1.5.1. Transmissible Spongiform Encephalopathy Certificate of Suitability to the monograph of the Pharmacopoeia of the Eurasian Economic Union or European Pharmacopoeia or a document issued by the competent authority for animal health of the county of origin where substances of animal origin are used, where appropriate.

1.5.2. The letter of the active substance master file holder committing to inform the manufacturer of the finished product and competent authority of the Member State on any modification before any significant amendments are made to the active substance master file (a certified copy of the letter signed of the qualified person certifying the quality of translation).

1.5.3. The active substance master file holder's permission to the competent authority to assess the data in the active substance master file upon its request (the Letter of Access).

1.5.4. Copy of a Certificate of Suitability to the monograph of the European Pharmacopoeia (where available).

1.5.5. Copy of a Plasma Master File Certificate issued by the competent authority of the manufacturer's own country (where available).

1.5.6. Copy of a Vaccine Antigen Master File issued by the competent authority of the manufacturer's own country (where available).

1.6. Documents on manufacturing

1.6.1. Properly certified copy of a valid document issued by the competent authority of the Member State, certifying compliance of the manufacturer (manufacturing site) of a medicinal product applied for granting a marketing authorization with the Requirements of the Eurasian Economic Union Good Manufacturing Practice subject to approval by the Commission (hereinafter referred to as Rules of Good Manufacturing Practice of the Union).

Properly certified copies of valid documents issued by the competent authorities of the country or countries where manufacturing site or manufacturing sites of different manufacturing steps is/are located and/or other competent authority or web-site of the Register of GMP certificates issued by the competent authorities (e.g. EudraGMDP) (where applicable), certifying compliance of the manufacturer with the Good Manufacturing Practice (hereinafter referred to as GMP).

1.6.2. Properly certified copies of a valid manufacturer's license for manufacturing of pharmaceuticals (together with annexes) issued by the competent authority of the country where manufacturing site or manufacturing sites of different manufacturing steps are located.

1.6.3. Properly certified copy of a manufacturing site(s) inspection report(s) on compliance with GMP carried out by the competent authority of a manufacturer's own country or other competent authority within previous 3 years together with a report on corrective actions and preventative actions (CAPA) taken following the inspection (where available) and the link to the competent authority GMP-inspection data base website (e.g. EudraGMDP) (where available).

1.6.4. Properly certified copy of an agreement between a medicinal product marketing authorization holder and a medicinal product manufacturer on GMP compliance issues where the medicinal product marketing authorization holder is not involved in manufacturing of the medicinal product (where available).

1.6.5. Properly certified copy of an agreement between a contract manufacturing site and a manufacturer on GMP compliance issues where the whole manufacturing process or any step of the manufacturing process is carried out on contract manufacturing site (where applicable).

1.6.6. Information on any regulatory action taken by the competent authority within previous 3 years based on the outcome of a manufacturing site inspection (where available).

1.6.7. A qualified person letter certifying compliance of the manufacturing of a medicinal product applied for marketing authorization with the Requirements of the Rules of the Good Manufacturing Practice of the Union including starting materials at each manufacturing site involved in the manufacturing of the finished product and of the active substance including sites where release testing or in-process testing is carried out. The letter shall be signed by the qualified person and certified by the manufacturer's seal and accompanied by the translation into Russian where necessary.

1.6.8. Information on product quality related complaints if those products have been manufactured by the manufacturing site where medicinal product applied for marketing authorization is to be manufactured, gathered within previous 3 years or evidence that no complaints exist.

1.6.9. The consent to be a subject of a pharmaceutical inspection for compliance with the requirements of international agreements and legal acts which constitute the law of the Union.

1.6.10. A copy of manufacturing site(s) master file certified by the applicant (where applicable).

1.6.11. The description of the finished product and active substance manufacturing process steps reflecting all manufacturing sites including testing sites.

1.7. Information about the Experts

1.7.1. Information about the Quality Expert

1.7.2. Information about the Non-clinical Expert

1.7.3. Information about the Clinical Expert

A declaration signed by the quality, non-clinical, or clinical expert drawn up respective overview and summaries together with brief information on their educational background, training and occupational experience. The experts shall have suitable technical or professional qualifications. The professional relationship of the expert to the applicant shall be declared.

1.8. Specific requirements for Different Types of Applications

1.8.1. A letter of a marketing authorization holder on an additional brand name of a medicinal product shall be provided where the applicant intends to apply for a marketing authorization using different brand names in the manufacturer's own country, reference Member State and Member State concerned (where applicable). The letter shall contain commitment that a single marketing authorization application dossier will be used for that purposes. The letter shall be signed and dated by the marketing authorization holder.

1.8.2. Information relating to Clinical Trials (where applicable)

1.8.2.1. Competent authority's authorization to commence a clinical trial, including the amendments made.

1.8.2.2. The list of GCP inspections carried out in respect of a medicinal product applied for a marketing authorization together with the list inspection authorities, dates of inspections, and the outcome thereof (where available).

The list of inspections shall include inspections clinical trial sites performed clinical trials of a medicinal product, inspections of sponsor and contract research organization premises, and inspections of other parties involved in performing clinical trials (e.g. analytical laboratories involved in clinical trials), other GCP inspections.

Where a clinical trial has been performed in clinical trial sites of third countries, the list shall include the outcome of GCP inspections carried out at clinical trial sites recruited the largest number of patients within investigation of a medicinal product concerned. Those inspections may concern other clinical trial including other medicinal product the marketing authorization holder of which is not the applicant. In this case, the competent authorities (assessment organizations) shall ask the appropriate regulatory authorities for reports of such inspections. These reports shall not be included in section 1.8.3.3 of Module 1.

1.8.2.3. Copies of reports on inspections listed in section 1.8.3.2. (where available)

1.8.2.4. Copies of agreements between a sponsor of a clinical trial and a clinical trial site (contract research organization) (after the confidential data is deleted where necessary).

1.8.3. Tabulated list of clinical trials (where applicable).

1.8.4. A letter of a marketing authorization holder on compliance of clinical trials of a medicinal product applied for a marketing authorization with the Requirements of the Rules of the Good Clinical Practice of the Eurasian Economic Union subject to approval by the Commission.

1.9. Applicant's documentation for the environmental risk assessment (in the form of Appendix to Module 1) (where available).

1.9.1. A letter of an applicant notifying that medicinal products contain or produced from genetically modified organisms (where applicable).

1.10. Information relating to applicant's pharmacovigilance activities in a Member State

1.10.1. Marketing authorization holder's pharmacovigilance system master file drawn up in accordance with the requirements of the Rules of the Good Pharmacovigilance Practice of the Eurasian Economic Union subject to approval by the Commission (hereinafter referred to as the Rules of the Good Pharmacovigilance Practice of the Union) shall be included where the marketing authorization holder applies for marketing authorization for a medicinal product in the Union for the first time.

Subsequent applications for marketing authorization of medicinal products by that marketing authorization holder a brief description of a marketing authorization holder' pharmacovigilance system shall be provided.

The brief description of a marketing authorization holder' pharmacovigilance system shall include following items:

- a written confirmation by the marketing authorization holder that there is a qualified person responsible for pharmacovigilance at his disposal. Where the marketing authorization holder is established outside the Member States, a written confirmation shall be included that there is a contact person for pharmacovigilance within the Member State;
- information on a Member State where the qualified person lives and perform their activities;
- contact details of the qualified person and of contact person (if applicable);
- declaration signed by the marketing authorization holder he is committed to perform activities and obligations listed in the Rules of the Good Pharmacovigilance Practice of the Union;
- link to the location (address) of the pharmacovigilance system master file.

1.10.2. A written confirmation by the marketing authorization holder that there is a qualified person responsible for pharmacovigilance at his disposal within a Member State.

1.10.3. The Risk Management Plan for a medicinal product applied for a marketing authorization drawn up in accordance with the Rules of the Good Pharmacovigilance Practice of the Union. The Risk Management Plan may be submitted electronically together with its summary in paper format (where applicable).

1.10.4. Properly certified written confirmation that more than one legal persons will respect all obligations of a marketing authorization holder where marketing authorization for a medicinal product was granted to different legal entities in the reference Member State and Member States concerned (where applicable).

1.11. Copies of documents confirming the trademark registration (where applicable).

2. Requirements for Module 2 of a marketing authorization application dossier: Summaries of Common Technical Document

This Module aims to summarize the chemical, pharmaceutical and biological data, the non-clinical data and the clinical data presented in Modules 3 to 5 of the dossier for marketing authorization, and to provide the conclusions of experts drawn up quality, non-clinical, and clinical summaries.

Factual summaries including tabular formats shall be provided. Those reports shall provide cross-references to tabular formats or to the information contained in the main documentation presented in Module 3 (Quality), Module 4 (non-clinical documentation) and Module 5 (clinical documentation).

The overviews and summaries shall comply with the basic principles and requirements as laid down herewith.

2.1. Table of contents of Modules 2 to 5

This section of the Module shall contain a table of contents for the documentation on quality, safety, and efficacy submitted in Modules 2 to 5.

2.2. Introduction to CTD

Information on the pharmacological class, mode of action and proposed clinical use of the medicinal product shall be supplied.

2.3. Quality overall summary

A review of the information related to the chemical, pharmaceutical and biological data shall be provided in a quality overall summary.

Key critical parameters and issues related to quality aspects shall be emphasized as well as justification in cases where the relevant requirements are not followed. This document shall follow the scope and outline of the corresponding detailed data presented in Module 3.

2.4. Non-clinical overview

An integrated and critical assessment of the non-clinical evaluation of the medicinal product in animal in vitro shall be required. Discussion and justification of the testing strategy and of deviation from the relevant requirements shall be included.

Except for biological medicinal products, an assessment of the impurities and degradation products shall be included along with their potential pharmacological and toxicological effects. The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the non-clinical studies and the product to be manufactured shall be discussed.

For herbal medicinal products, biological medicinal products, comparability of material used in non-clinical studies, clinical studies, and the medicinal product for marketing shall be assessed.

Any novel excipient shall be the subject of a specific safety assessment.

The characteristics of the medicinal product, as demonstrated by the non-clinical studies shall be defined and the implications of the findings for the safety of the medicinal product for the intended clinical use in human shall be discussed.

2.5. Clinical overview

The clinical overview is intended to provide a critical analysis of the clinical data included in the clinical summary and Module 5. The approach to the clinical development of the medicinal product, including critical study design, decisions related to and performance of the studies shall be provided.

A brief overview of the clinical findings, including important limitations as well as an evaluation of benefits and risks based on the conclusions of the clinical studies shall be provided. An interpretation of the way the efficacy and safety findings support the proposed dose and target indications and an evaluation of how the summary of product characteristics, patient leaflet, and other approaches will optimize the benefits and manage the risks is required.

Efficacy or safety issues encountered in development and unresolved issues shall be explained.

2.6. Non-clinical summary

The results of pharmacology, pharmaco-kinetics and toxicology studies carried out in animals in vitro shall be provided as factual written and tabulated summaries which shall be presented in the following order together with the introduction.

2.6.1. Pharmacology Written Summary
2.6.2. Pharmacology Tabulated Summary
2.6.3. Pharmacokinetics Written Summary
2.6.4. Pharmacokinetics Tabulated Summary
2.6.5. Toxicology Written Summary
2.6.6. Toxicology Tabulated Summary.

2.7. Clinical Summary

A detailed, factual summary of the clinical information on the medicinal product included in Module 5 shall be provided. This shall include the results of all bio-pharmaceutics studies, of clinical pharmacology studies, and of clinical efficacy and safety studies. A synopsis of the individual studies is required.

Summarized clinical information shall be presented in the following order together with list of literature references.

2.7.1. Summary of Biopharmaceutics and Associated Analytical Methods
2.7.2. Summary of Clinical Pharmacology Studies
2.7.3. Summary of Clinical Efficacy
2.7.4. Summary of Clinical Safety
2.7.5. Copies of literature references used
2.7.6. Synopses of Individual Studies

3. Requirements for Module 3 of a marketing authorization application dossier: Quality

3.1. Table of contents of Module 3

3.2. Basic principles and requirements

a) The chemical, pharmaceutical and biological data that shall be provided shall include for the active substance(s) and for the finished medicinal product all of relevant information on: the development, the manufacturing process, the characterization and properties, the quality control operations and requirements, the stability as well as a description of the composition and packaging of the finished medicinal product.

b) Main sets of information shall be provided, dealing with the active substance(s) and with the finished medicinal product, respectively.

c) Detailed information on the starting and raw materials used during the manufacturing operations of the active substance(s) and on the excipients incorporated in the formulation of the finished medicinal product shall be supplied.

d) All the procedures and methods used for manufacturing and controlling the active substance and the finished medicinal product shall be described in sufficient details to enable them to be repeated in control tests, carried out at the request of the competent authority of the reference Member State. All test procedures shall correspond to the state of scientific progress at the time and shall be validated. Results of the validation studies shall be provided. In the case of test procedures included in the Pharmacopoeia of the Eurasian Economic Union or pharmacopoeias of Member States or main pharmacopeias in accordance with the Eurasian Economic Union Member States Pharmacopeia Harmonization Conception (hereinafter referred to as the Conception), this description shall be replaced by the appropriate detailed reference to the monograph(s) and general chapter(s).

e) For all active substances mentioned in the Pharmacopoeia of the Eurasian Economic Union or pharmacopoeias of Member States or main pharmacopeias in accordance with the Conception, the reference to the aforementioned pharmacopeias shall be provided.

However, where an active substance included in the Pharmacopoeia of the Eurasian Economic Union or pharmacopoeias of Member States or main pharmacopeias in accordance with the Conception has been prepared by a method liable to leave impurities not controlled in the pharmacopoeia monograph, these impurities and their maximum tolerance limits must be declared and a suitable test procedure must be described. In cases where a specification contained in a monograph of the Pharmacopoeia of the Eurasian Economic Union or pharmacopoeias of Member States or main pharmacopeias in accordance with the Conception might be insufficient to ensure the quality of the substance, more appropriate specifications from the manufacturer or marketing authorization holder might be required.

In the case of analytical procedures included in the Eurasian Economic Union, this description shall be replaced in each relevant section by the appropriate detailed reference to the monograph(s) and general chapter(s).

f) In case where starting and raw materials, active substance(s) or excipient(s) are described neither in the Pharmacopoeia of the Eurasian Economic Union nor pharmacopoeias of Member States nor main pharmacopeias in accordance with the Conception, compliance with the monograph of a third country pharmacopoeia can be accepted. In such cases, the applicant shall submit a copy of the monograph accompanied by the validation of the analytical procedures contained in the monograph and by a translation where appropriate.

g) Where the active substance and/or a starting material or excipient(s) are the subject of a monograph of the European Pharmacopoeia, the applicant can apply for a certificate of suitability that shall be presented in the relevant section of this Module. Those certificates of suitability of the monograph of the European Pharmacopoeia are deemed to replace the relevant data of the corresponding sections described in this Module. The manufacturer of the active substance shall give the assurance in writing to the applicant that the manufacturing process has not been modified since the granting of the certificate of suitability.

h) For a well-defined active substances (which have been in well-established medicinal use for at least ten years from the first systematic and documented use of that active substance(s) as a medicinal product within at least 3 Member States), the active substance manufacturer or the applicant may arrange for the

- detailed description of the manufacturing process,
- quality control during manufacture, and
- process validation

to be supplied in a separate document directly to the competent authority of the Member State by the manufacturer of the active substance as an Active Substance Master File.

In case of using active substance master file within the marketing authorization application dossier, the manufacturer shall, however, provide the applicant (marketing authorization holder) with all of the data, which may be necessary for the latter to take responsibility for the medicinal product provided by these Rules. The manufacturer shall confirm in writing to the applicant (marketing authorization holder) that he shall ensure batch to batch consistency and not modify the manufacturing process or specifications without informing the applicant (marketing authorization holder). Documents and particulars supporting the application for such a change shall be supplied to the competent authority; these documents and particulars will be also supplied to the applicant when they concern the open part of the active substance master file.

Where an applicant does not have full information on the closed part of the active substance master file being of confidential nature, the application shall be accompanied with the Letter of Access issued by the active substance manufacturer where the information of that active substance has been included in the Common Register. Such a Letter of Access shall authorize using the previously submitted closed part of the active substance master file within the assessment of a medicinal product by the competent authority;

i) Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies (materials from ruminant origin): at each step of the manufacturing process, the applicant must demonstrate the compliance of the materials used with the Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products, published in the Pharmacopeia of the Eurasian Economic Union or must submit either a certificate of suitability to the relevant monograph of the European Pharmacopoeia or by the supply of scientific data to substantiate this compliance.

j) For adventitious agents, information assessing the risk with respect to potential contamination with adventitious agents, whether they are non-viral or viral, as laid down in relevant guidelines as well as in relevant general monograph and general chapter of the Pharmacopoeia of the Eurasian Economic Union nor pharmacopoeias of Member States nor main pharmacopeias in accordance with the Conception, shall be provided.

k) Any special apparatus and equipment, which may be used at any stage of the manufacturing process and control operations of the medicinal product, shall be described in adequate details.

l) Where needed, an evidence of marketing authorization for a medical device in accordance with the rules subject to approval by the Commission shall be provided.

3.2.S. Active substance

3.2.S.1. General information and information related to the starting and raw materials

a) Information on the nomenclature of the active substance shall be provided, including recommended International Non-proprietary Name (INN), Pharmacopoeia of the Eurasian Economic Union name and chemical name(s) using IUPAC nomenclature.

The structural formula, including relative and absolute stereo-chemistry, the molecular formula, and the relative molecular mass shall be provided. For biotechnological medicinal products if appropriate, the schematic amino acid sequence and relative molecular mass shall be provided.

A list shall be provided of physicochemical and other relevant properties of the active substance, including biological activity for biological medicinal products.

3.2.S.2. Manufacturing process of the active substance

a) The applicant shall provide the description of the active substance manufacturing process. To adequately describe the manufacturing process and process controls, appropriate information as laid down in respective documents which constitute the law of the Union.

b) All materials needed in order to manufacture the active substance shall be listed, identifying where each starting or raw material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided. Raw materials shall be listed and their quality and controls shall also be documented. The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing shall be provided.

c) For biological medicinal products, the following additional requirements shall apply:

the origin and history of starting materials shall be described and documented;

regarding the specific measures for the prevention of the Transmission of animal Spongiform Encephalopathies, the applicant must demonstrate that the active substance complies with the Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published in the Pharmacopoeia of the Eurasian Economic Union;

- when cell banks are used, the cell characteristics shall be shown to have remained unchanged at the passage level used for the production and beyond;
- seed materials, cell banks, pools of serum or plasma and other materials of biological origin and, whenever possible, the materials from which they are derived shall be tested for adventitious agents;
- if the presence of potentially pathogenic adventitious agents is inevitable, the corresponding material shall be used only when further processing ensures their elimination and/or inactivation, and this shall be validated;
- whenever possible, vaccine production shall be based on a seed lot system and on established cell banks. For bacterial and viral vaccines, the characteristics of the infectious agent shall be demonstrated on the seed. In addition, for live vaccines, the stability of the attenuation characteristics shall be demonstrated on the seed; if this proof is not sufficient, the attenuation characteristics shall also be demonstrated at the production stage;
- for medicinal products derived from human blood or plasma, the origin and the criteria and procedures for collection, transportation and storage of the starting material shall be described and documented in accordance with provisions laid down in Part III of this Appendix.
- the manufacturing facilities and equipment shall be described.

d) Tests and acceptance criteria carried out at every critical step, information on the quality and control of intermediates and process validation and/or evaluation studies shall be provided as appropriate.

e) If the presence of potentially pathogenic adventitious agents is inevitable, the correspondent material shall be used only when further processing ensures their elimination and/or inactivation and this shall be validated in the section dealing with viral safety evaluation.

f) A description and discussion of the significant changes made to the manufacturing process during development and/or manufacturing site of the active substance shall be provided. In addition, where the finished product manufacturer is not an active substance manufacturer, the active substance manufacturer shall provide a copy of their written obligation to notify the applicant on changes to the manufacturing process and to the specifications using any format.

3.2.S.3. Characterization of the active substance

- Data highlighting the structure and other characteristics of the active substance(s) shall be provided.
- Confirmation of the structure of the active substance(s) based on any physicochemical and/or immuno-chemical and/or biological methods, as well as information on impurities shall be provided.

3.2.S.4. Control of active substance

- Detailed information on the specifications used for routine control of active substance, justification for the choice of these specifications, methods of analysis and their validation shall be provided.

- The results of control carried out on individual batches manufactured during development shall be presented.

3.2.S.5. Reference standards or materials

- Reference preparations and standards shall be identified and described in detail. Where relevant, pharmacopoeial chemical reference standards and biological reference materials shall be used.

3.2.S.6. Container and closure system

- A description of the container and the closure system(s) and their specifications shall be provided.

3.2.S.7. Stability

a) The types of studies conducted, protocol used, and the results of the studies shall be summarized;

b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format;

c) The post authorization stability protocol and stability commitment shall be provided.

3.2.P. Finished medicinal product

3.2.P.1. Description and composition of the finished medicinal product

A description of the finished medicinal product and its composition shall be provided. The information shall include the description of the pharmaceutical form and composition with all the constituents of the finished medicinal product, their amount on a per-unit basis, the function of the constituents of:

- the active substance,
- the constituent(s) of the excipients, whatever their nature or the quantity used, including coloring matter, preservatives, adjuvants, stabilizers, thickeners, emulsifiers, flavoring and aromatic substances, etc.,
- the constituents, intended to be ingested or otherwise administered to the patient, of the outer covering of the medicinal products (hard capsules, soft capsules, rectal capsules, coated tablets, films-coated tablets, etc.),

these particulars shall be supplemented by any relevant data concerning the type of container and, where appropriate, its manner of closure, together with details of devices with which the medicinal product will be used or administered and which will be delivered with the medicinal product.

The ‘usual terminology’, to be used in describing the constituents of medicinal products, shall mean, notwithstanding the application of the other provisions:

- in respect of substances which have INN recommended World Health Organization, INN or where a substance is in its salt, ether, ester, hydrate or other form, respective modified INN,
- in respect of other substances (where no INN exist), the usual common name taking into account alt, ether, ester, hydrate or other form; where no usual common name exist, chemical name using IUPAC nomenclature; where no such a name exist, a statement of how and from what they were prepared, supplemented, where appropriate, by any other relevant details shall be provided,
- in respect of coloring matter, designation by the ‘E’ code assigned to them in International Numbering System for Food Additives of the Codex Alimentaruis.

In order to give the ‘quantitative composition’ of the active substance of the finished medicinal products, it is necessary, depending on the pharmaceutical form concerned, to specify the mass, or the number of units of biological activity, either per dosage-unit or per unit of mass or volume, of each active substance.

Active substances present in the form of compounds or derivatives shall be designated quantitatively by their total mass, and if necessary or relevant, by the mass of active entity where necessary.

For medicinal products containing an active substance, which is the subject of an application for marketing authorization for the first time, the quantitative statement of an active substance, which is a salt or hydrate shall be systematically expressed in terms of the mass of the active

entity or entities in the molecule. All subsequently authorized medicinal products in the Member States shall have their quantitative composition stated in the same way for the same active substance.

For medicinal products containing an active substance, which is the subject of an application for marketing authorization for the first time, the quantitative statement of an active substance, which is a salt or hydrate shall be systematically expressed in terms of the mass of the active entity or entities in the molecule. All subsequently authorized medicinal products in the Member States shall have their quantitative composition stated in the same way for the same active substance.

Units of biological activity shall be used for substances, which cannot be defined molecularly. Where an International Unit of biological activity has been defined by the World Health Organization, this shall be used. Where no International Unit has been defined, the units of biological activity shall be expressed in such a way as to provide unambiguous information on the activity of the substances by using where applicable Units of the Pharmacopoeia of the Eurasian Economic Union.

3.2.P.2. Pharmaceutical development

This section shall be devoted to information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the intended use specified in the marketing authorization application dossier.

The studies described in this section are distinct from routine control tests conducted according to specifications. Critical parameters of the formulation and process attributes that can influence batch reproducibility, medicinal product performance and medicinal product quality shall be identified and described. Additional supportive data, where appropriate, shall be referenced to the relevant chapters of Modules 4 and 5.

- The compatibility of the active substance with excipients as well as key physicochemical characteristics of the active substance that can influence the performance of the finished product or the compatibility of different active substances with each other in the case of combination products, shall be documented.
- The choice of excipients, in particular relative to their respective functions and concentration shall be documented.
- A description of the development of the finished product shall be provided, taking into consideration the proposed route of administration and usage.
- Any overages in the formulation shall be warranted.
- As far as the physiochemical and biological properties are concerned, any parameter relevant to the performance of finished product shall be addressed and documented.
- The selection and optimization of the manufacturing process as well as differences between the manufacturing process(es) used to produce pivotal clinical batches and the process used for manufacturing the proposed finished medicinal product shall be provided.
- The suitability of the container and closure system used for the storage, shipping and use of the finished product shall be documented. A possible interaction between medicinal product and container may need to be considered.
- The microbiological attributes of the dosage form in relation with non-sterile and sterile products shall be in accordance with and documented as prescribed in the Pharmacopoeia of the Eurasian Economic Union.
- In order to provide appropriate and supportive information for the labelling the compatibility of the finished product with reconstitution diluent(s) or dosage devices shall be documented.

3.2.P.3. Manufacturing process of the finished medicinal product

a) The description of the manufacturing method shall be drafted in such a way as to give an adequate synopsis of the nature of the operations employed.

For this purpose, it shall include at least:

- description of the various stages of manufacture including process controls and corresponding acceptance criteria, so that an assessment can be made of whether the processes

employed in producing the pharmaceutical form might have produced an adverse change in the constituents,

- in the case of continuous manufacture, full details concerning precautions taken to ensure the homogeneity of the finished product,

- experimental studies validating the manufacturing process, where a non-standard method of manufacture is used or where it is critical for the product,

- for sterile medicinal products, details of the sterilization processes and/or aseptic procedures used,

- a detailed batch formula.

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or laboratory involved in manufacturing and testing shall be provided.

b) Particulars relating to the product control tests that may be carried out at an intermediate stage of the manufacturing process, with a view to ensuring the consistency of the production process shall be included.

These tests are essential for checking the conformity of the medicinal product with the formula when, exceptionally, an applicant proposes an analytical method for testing the finished product which does not include the assay of all the active substances (or of all the excipient constituents subject to the same requirements as the active substances).

The same applies where the quality control of the finished product depends on in-process control tests, particularly if the quality of the medicinal product is essentially defined by its method of preparation.

c) Description, documentation, and results of the validation studies for critical steps or critical assays used in the manufacturing process shall be provided.

3.2.P.4. Control of excipients

a) All the materials needed in order to manufacture the excipient(s) shall be listed identifying where each material is used in the process. Information on the quality and control of these materials shall be provided. Information demonstrating that materials meet standards appropriate for their intended use shall be provided.

Coloring matter shall, in all cases, satisfy the requirements of the monographs of the Pharmacopoeia of the Eurasian Economic Union and the requirements of the Technical Regulation of the Customs Union ‘Safety Requirements for Food Additives, Flavorings, and Technological Aides’ (TP TC 029/2012) adopted by the Decision of the Council of the Commission of 20 July 2012 N 58; in addition coloring matter shall meet purity criteria as laid down in the requirements of legal acts which constitute the law of the Union.

b) For each excipient, the specifications and their justifications shall be detailed. The analytical procedures used for their quality control shall be described and duly validated.

Specific attention shall be paid to excipients of human or animal origin.

Regarding the specific measures for the prevention of the Trans-mission of animal Spongiform Encephalopathies, the applicant must demonstrate also for excipients that the medicinal product is manufactured in accordance with the Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products and its updates, published the Pharmacopoeia of the Eurasian Economic Union.

Demonstration of compliance with the aforementioned Guidance can be done by submitting either preferably a certificate of suitability to the relevant monograph on Transmissible Spongiform Encephalopathies of the European Pharmacopoeia, or by the supply of scientific data to substantiate this compliance.

d) Novel excipients:

For excipients used for the first time in a medicinal product or by a new route of administration, full details of manufacture, characterization, and controls, with cross references to supporting safety data, both non-clinical and clinical, shall be provided according to the active substance format previously described.

A document containing the detailed chemical, pharmaceutical and biological information shall be presented. This information shall be formatted in the same order as the chapter devoted to Active Substance of Module 3.

Information on a novel excipient may be presented as a standalone document following the format described in the former paragraphs.

Where the applicant differs from the novel excipient manufacturer the said stand-alone document shall be made available to the applicant for submission to the competent authority.

Additional information on toxicity studies with the novel excipient shall be provided in Module 4 of the dossier.

Clinical studies data on a new excipient shall be provided in Module 5.

3.2.P.5. Control of the finished medicinal product

For the control of the finished medicinal product, a batch of a medicinal product is an entity which comprises all the units of a pharmaceutical form which are made from the same initial quantity of raw materials and materials and have undergone the same series of manufacturing and/or sterilization operations or, in the case of a continuous production process, all the units manufactured in a given period of time and which are homogeneous.

Unless there is appropriate justification, the maximum acceptable deviation in the active substance content of the finished product shall not exceed ± 5 % at the time of manufacture.

Detailed information on the specifications, (release and shelf life based on stability studies) justification for their choice, methods of analysis and their validation shall be provided.

3.2.P.6. Reference standards or materials

Reference preparations and standards used for testing of the finished medicinal product shall be identified and described in detail, if not previously provided in the section related to the active substance.

3.2.P.7. Container and closure

A description of the container and the closure system(s) including the identity of each immediate packaging material and their specifications shall be provided. The specifications shall include description and identification. Non-pharmacopoeial methods (with validation) shall be included where appropriate.

For non-functional outer (user) packaging materials only a brief description shall be provided. For functional outer (user) packaging materials additional information shall be provided.

3.2.P.8. Stability of the finished medicinal product

a) The types of studies conducted, protocols used, and the results of the studies shall be summarised;

b) Detailed results of the stability studies, including information on the analytical procedures used to generate the data and validation of these procedures shall be presented in an appropriate format;

in case of vaccines, information on cumulative stability shall be provided where appropriate;

c) The post authorization stability protocol and stability commitment shall be provided.

3.2.A. Appendices

3.2.A.1. Facilities and Equipment

3.2.A.2. Adventitious Agents Safety Evaluation

3.2.A.3. Novel Excipients

3.2.R.1. Manufacturing Site Master File

3.2.R.2. Process Validation Scheme for the Drug Product

3.2.R.3. The Latest Finished Medicinal Product Quality Review

3.2.R.4. Quality Manual or Manufacturer's Quality Control Laboratory Manual

3.2.R.5. List of Test Procedures Carried Out by the Manufacturer's Quality Control Laboratory

4. Requirements for Module 4 of a marketing authorization application dossier: Non-clinical (preclinical) reports

4.1. Table of Content of Module 4

4.2. Non-clinical (preclinical) reports

In specific circumstances and in accordance with the requirements for investigation of specific groups of medicinal products described in Part II to these Requirements and Rules of authorization and assessment of medicinal products for human use subject to approval by the

Commission, this section might contain scientific review in place of own data on non-clinical testing.

The pharmacological and toxicological tests must show:

- the potential toxicity of the product and any dangerous or undesirable toxic effects that may occur under the proposed conditions of use in human beings; these should be evaluated in relation to the pathological condition concerned;
- the pharmacological properties of the product, in both qualitative and quantitative relationship to the proposed use in human beings. All results must be reliable and of general applicability. Whenever appropriate, mathematical and statistical procedures shall be used in designing the experimental methods and in evaluating the results.

Additionally, it is necessary for clinicians to be given information about the therapeutic and toxicological potential of the product.

For biological medicinal products such as immunological medicinal products and medicinal products derived from human blood or plasma, the requirements of this Module may have to be adapted for individual products; therefore the testing program carried out shall be justified by the applicant.

In establishing the testing program, the following shall be taken into consideration:

- all tests requiring repeated administration of the product shall be designed to take account of the possible induction of, and interference by, antibodies;
- examination of reproductive function, of embryo/foetal and perinatal toxicity, of mutagenic potential and of carcinogenic potential shall be considered. Where constituents other than the active substance(s) are incriminated, validation of their removal may replace the study.

The toxicology and pharmacokinetics of an excipient used for the first time in the pharmaceutical field shall be investigated in terms of it pharmacology and toxicology.

Where there is a possibility of significant degradation during storage of the medicinal product, the toxicology of degradation products must be considered.

4.2.1. Pharmacology

In terms of pharmacology study the marketing authorization application dossier shall follow two distinct lines of approach.

- the actions relating to the proposed therapeutic use shall be adequately investigated and described. Where possible, recognized and validated assays, both in vivo and in vitro, shall be used. Novel experimental techniques must be described in such detail as to allow them to be reproduced. The results shall be expressed in quantitative terms using, for example, dose-effect curves, time-effect curves, etc. Wherever possible, comparisons shall be made with data relating to a substance or substances with a similar therapeutic action. Where no comparative data exists, it shall be justified;
- the applicant shall investigate the potential undesirable pharmacodynamic effects of the substance on physiological functions. These investigations shall be performed at exposures in the anticipated therapeutic range and above. The experimental techniques, unless they are standard procedures, must be described in such detail as to allow them to be reproduced, and the investigator must establish their validity. Any quantitative modification of responses resulting from repeated administration of the substance shall be investigated.

For the pharmacodynamic medicinal product interaction, tests on combinations of active substances may be prompted either by pharmacological premises or by indications of therapeutic effect. In the first case, the pharmacodynamic study shall demonstrate those interactions, which might make the combination of value in therapeutic use. In the second case, where scientific justification for the combination is sought through therapeutic experimentation, the investigation shall determine whether the effects expected from the combination can be demonstrated in animals, and the importance of any collateral effects shall at least be investigated.

4.2.2. Pharmacokinetics

Pharmacokinetics means the study of the fate of the active substance, and its metabolites, within the organism, and covers the study of the absorption, distribution, biotransformation and excretion of the active substance and its metabolites.

The study of these phases (absorption, distribution, biotransformation and excretion) may be carried mainly by means of physical, chemical or possibly by biological methods, and by observation of the actual pharmacodynamic activity of the active substance itself.

Information on distribution and elimination shall be necessary in all cases where such data are indispensable to determine the dosage for humans, and in respect of chemo-therapeutic substances (antibiotics, etc.) and substances whose use depends on their non-pharmacodynamic effects (e.g. numerous diagnostic agents, etc.).

In vitro studies also can be carried out with the advantage of using human material for comparison with animal material (i.e. protein binding, metabolism, drug-drug interaction).

The marketing authorization application shall contain the data on pharmacokinetic investigation of all pharmacologically active substances. In the case of new combinations of known substances, which have been investigated in accordance with the provisions of the legal acts governing medicinal products which constitute the law of the Union, pharmacokinetic studies may not be required, if the toxicity tests and therapeutic experimentation justify their omission.

The pharmacokinetic program shall be design to allow comparison and extrapolation between animal and human.

4.2.3. Toxicology

4.2.3.1. Single-dose toxicity of the active substance

A single-dose toxicity test shall mean a qualitative and quantitative study of the toxic reactions, which may result from a single administration of the active substance or substances contained in the medicinal product, in the proportions and physicochemical state in which they are present in the actual product.

The single-dose toxicity test must be carried out in accordance with the relevant guidelines published by the Commission or, in absence thereof, by Member States.

4.2.3.2. Repeat-dose toxicity

Repeated dose toxicity tests are intended to reveal any physiological and/or anatomo-pathological changes induced by repeated administration of the active substance or combination of active substances under examination, and to determine how these changes are related to dosage.

Generally, it is desirable that two tests be performed: one short term, lasting two to four weeks, the other long-term.

The duration of the long-term test shall depend on the conditions of clinical use of the medicinal product.

Its purpose is to describe potential adverse effects to which attention should be paid in clinical studies.

The duration is defined in the relevant guidelines published by the Commission or, in absence thereof, by Member States.

4.2.3.3. Genotoxicity

The purposes of the study of mutagenic and clastogenic potential is to reveal the changes which a substance may cause in the genetic material of individuals or cells. Mutagenic substances may present a hazard to health since exposure to a mutagen carries the risk of inducing germline mutation, with the possibility of inherited disorders, and the risk of somatic mutations including those leading to cancer. These studies are obligatory for any new substance.

4.2.3.4. Carcinogenicity

Tests to reveal carcinogenic effects shall normally be required:

for any medicinal product whose expected clinical use is for a prolonged period of a patient's life, either continuously or repeatedly in an intermittent manner;

evidence of preneoplastic lesions in repeated dose toxicity studies;

for some active substances if there is concern about their carcinogenic potential or co-carcinogenic potential, e.g. from product of the same class or similar structure, or from evidence in repeated dose toxicity studies.

Studies with unequivocally genotoxic compounds are not needed, as they are presumed to be trans-species carcinogens, implying a hazard to humans. If such a medicinal product is intended to be administered chronically to humans a chronic study may be necessary to detect early tumorigenic effects.

4.2.3.5. Reproductive and developmental toxicity

Investigation of possible impairment of male or female reproductive function as well as harmful effects on progeny shall be performed by appropriate tests.

These tests comprise studies of effect on adult male or female reproductive function, studies of the toxic and teratogenic effects at all stages of development from conception to sexual maturity as well as latent effects, when the medicinal product under investi-gation has been administered to the female during pregnancy.

Omission of these tests must be adequately justified.

Depending on the indicated use of the medicinal product, additional studies addressing development when administering the medicinal product of the offspring may be warranted.

Embryo/foetal toxicity studies shall normally be conducted on two mammalian species, one of which shall be other than a rodent. Peri- and postnatal studies shall be conducted in at least one species.

If the metabolism of a medicinal product in particular species is known to be similar to that in man, it is desirable to include this species.

It is also desirable that one of the species is the same as in the repeated dose toxicity studies.

The state of scientific knowledge at the time when the application is lodged shall be taken into account when determining the study design.

4.2.3.6. Local tolerance

The purpose of local tolerance studies is to ascertain whether medicinal products (both active substances and excipients) are tolerated at sites in the body, which may come into contact with the medicinal product as a result of its administration in clinical use.

The testing strategy shall be such that any mechanical effects of administration or purely physicochemical actions of the product can be distinguished from toxicological or pharmacodynamic ones.

Local tolerance testing shall be conducted with the preparation being developed for human use, using the vehicle and/or excipients in treating the control group(s). Positive controls/reference substances shall be included where necessary.

The design of local tolerance tests (choice of species, duration, frequency and route of administration, doses) will depend upon the problem to be investigated and the proposed conditions of administration in clinical use. Reversibility of local lesions shall be performed where relevant.

Studies in animals can be substituted by validated in vitro tests provided that the test results are of comparable quality and usefulness for the purpose of safety evaluation.

For chemicals applied to the skin (e.g. dermal, rectal, vaginal) the sensitizing potential shall be evaluated in at least one of the test systems currently available (the guinea pig assay or the local lymph node assay).

5. Requirements for Module 5 of a marketing authorization application dossier: Clinical reports

5.1. Table of Content of Module 5

5.2. Content: basic principles and requirements

Special attention shall be paid to the following selected elements.

a) The clinical particulars to be provided must enable a sufficiently well-founded and scientifically valid opinion to be formed as to whether the medicinal product satisfies the criteria governing the granting of a marketing authorization. Consequently, an essential requirement is that the results of all clinical trials should be communicated, both favorable and unfavorable.

b) Clinical trials must always be preceded by adequate pharmacological and toxicological tests, carried out on animals data of which shall be provided in Module 4. The investigator must acquaint himself with the conclusions drawn from the pharmacological and toxicological studies and hence the applicant must provide him at least with the investigator's brochure, consisting of all the relevant information known prior to the onset of a clinical trial including chemical, pharmaceutical and biological data, toxicological, pharmacokinetic and pharmacodynamic data in

animals and the results of earlier clinical trials, with adequate data to justify the nature, scale and duration of the proposed trial; the complete pharmacological and toxicological reports shall be provided on request. For materials of human or animal origin, all available means shall be employed to ensure safety from transmission of infectious agents prior to the commencement of the trial.

c) Marketing authorization holder must arrange for essential clinical trial documents (including case report forms) other than subject's medical files, to be kept by the owners of the data:

- for at least 15 years after completion or discontinuation of the trial,
- for at least two years after the granting of the last marketing authorization in the Union and when there are no pending or contemplated marketing applications,
- for at least two years after formal discontinuation of clinical development of the investigational product.

Subject's medical files should be retained in accordance with applicable legislation of the Member State and in accordance with the maximum period of time permitted by the hospital, institution or private practice.

The documents can be retained for a longer period, however, if required by the applicable regulatory requirements or by agreement with the sponsor.

It is the responsibility of the sponsor to inform the hospital, institution or practice as to when these documents no longer need to be retained.

The sponsor or other owner of the data shall retain all other docu-mentation pertaining to the trial as long as the product is authorized.

This documentation shall include:

- the protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product, the reference medicinal product and/or the placebo used;
- standard operating procedures;
- all written opinions on the protocol and procedures; the investigator's brochure; case report forms on each trial subject;
- final report;
- audit certificate(s), if available.

The final report shall be retained by the sponsor or subsequent owner, for five years after the medicinal product is no longer authorized.

In addition, for trials conducted within the European Community, the marketing authorization holder shall make any additional arrangements for archiving of documentation in accordance with the provisions of the Rules of Good Clinical Practice of the Eurasian Economic Union and implementing detailed guidelines.

Any change of ownership of the data shall be documented.

All data and documents shall be made available if requested by relevant authorities.

d) The particulars of each clinical trial must contain sufficient detail to allow an objective judgement to be made:

- the protocol, including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational medicinal product used;
- audit certificate(s), if available;
- the list of investigator(s), and each investigator shall give his name, address, appointments, qualifications and clinical duties,
- shall state where the trial was carried out,
- shall assemble the information in respect of each patient individually, including case report forms on each trial subject;
- final report signed by the investigator and for multicenter trials, by all the investigators or the coordinating (principal) investigator.

e) The particulars of clinical trials referred to in subparagraphs a to d shall be forwarded to the competent authorities. However, in agreement with the competent authorities, the applicant may omit part of this information. Complete documentation shall be provided forthwith upon request.

The investigator shall, in his conclusions on the experimental evidence, express an opinion on the safety of the product under normal conditions of use, its tolerance, its efficacy and any useful information relating to indications and contra-indications, dosage and average duration of treatment as well as any special precautions to be taken during treatment and the clinical symptoms of over dosage.

In reporting the results of a multicenter study, the principal investigator shall, in his conclusions, express an opinion on the safety and efficacy of the investigational medicinal product on behalf of all centers.

f) The clinical observations shall be summarized for each trial indicating:

- the number and sex of subjects treated;
- the selection and age-distribution of the groups of patients being investigated and the comparative tests;
- the number of patients withdrawn prematurely from the trials and the reasons for such withdrawal;
- where controlled trials were carried out under the above conditions, whether the control group: received no treatment, received a placebo, received another medicinal product of known effect, received treatment other than therapy using medicinal products;
- the frequency of observed adverse reactions;
- details concerning patients who may be at increased risk, e.g. elderly people, children, women during pregnancy or menstru-ation, or whose physiological or pathological condition requires special consideration;
- parameters or evaluation criteria of efficacy and the results in terms of these parameters;
- a statistical evaluation of the results when this is called for by the design of the trials and the variable factors involved.

g) In addition, the investigator shall always indicate his observations on:

- any signs of habituation, addiction or difficulty in weaning patients from the medicinal product;
- any interactions that have been observed with other medicinal products administered concomitantly;
- the criteria determining exclusion of certain patients from the trials;
- any deaths which occurred during the trial or within the follow-up period.

h) Particulars concerning a new combination of medicinal substances must be identical to those required for new medicinal products and must substantiate the safety and efficacy of the combination.

i) Total or partial omission of data required under subparagraphs a to h must be explained.

Should unexpected results occur during the course of the trials, further preclinical toxicological and pharmacological tests must be undertaken and reviewed.

j) If the medicinal product is intended for long-term administration, particulars shall be given of any modification of the pharmacological action following repeated administration, as well as the establishment of long-term dosage.

5.3. Clinical reports

5.3.1. Reports of biopharmaceutics studies

Bioavailability study reports, comparative bioavailability, bioequivalence study reports, reports on in vitro and in vivo correlation study, and bioanalytical and analytical methods shall be provided.

An assessment of comparative bioavailability shall be undertaken where necessary to demonstrate bioequivalence for the medicinal products.

In case of biowaiver, an in vitro studies report shall be provided in the marketing authorization application dossier. Evaluation and performance of bioequivalence studies of justification for waiving bioequivalence studies shall be in accordance with the requirements of the Rules of performing bioequivalence studies of medicinal products in the Eurasian Economic Union subject to approval by the Commission.

5.3.2. Reports of studies pertinent to pharmacokinetics using human bio-materials

Human bio-materials shall mean any proteins, cells, tissues and related materials derived from human sources that are used in vitro or ex vivo to assess pharmacokinetics properties of active substances.

In this respect, reports of plasma protein binding study, hepatic metabolism and active substance interaction studies and studies using other human biomaterials shall be provided.

5.3.3. Reports of human pharmacokinetic studies

- The following pharmacokinetic characteristics shall be described:
  absorption (rate and extent),
- distribution,
- metabolism,
- excretion.

Clinically significant features including the implication of the kinetic data for the dosage regimen especially for patients at risk, and differences between man and animal species used in the preclinical studies, shall be described.

In addition to standard multiple-sample pharmacokinetics studies, population pharmacokinetics analyses based on sparse sampling during clinical studies can also address questions about the contributions of intrinsic and extrinsic factors to the variability in the dose-pharmacokinetics response relationship.

Reports of pharmacokinetic and initial tolerability studies in healthy subjects and in patients, reports of pharmacokinetic studies to assess effects of intrinsic and extrinsic factors, and reports of population pharmaco-kinetic studies shall be provided.

If the medicinal product is normally to be administered concomitantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

Pharmacokinetic interactions between the active substance and other medicinal products or substances shall be investigated.

5.3.4. Reports of human pharmacodynamic studies

a) The pharmaco-dynamic action correlated to the efficacy shall be demonstrated including:

- the dose-response relationship and its time course,
- justification for the dosage and conditions of administration,
- the mode of action, if possible.

The pharmacodynamic action not related to efficacy shall be described.

The demonstration of pharmacodynamic effects in human beings shall not in itself be sufficient to justify conclusions regarding any particular potential therapeutic effect.

b) If the medicinal product is normally to be administered concomi-tantly with other medicinal products, particulars shall be given of joint administration tests performed to demonstrate possible modification of the pharmacological action.

Pharmacodynamic interactions between the active substance and other medicinal products or substances shall be investigated.

5.3.5. Reports of efficacy and safety studies

5.3.5.1. Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indications

In general, clinical trials shall be done as ‘controlled clinical trials’ if possible, randomized and as appropriate versus placebo and/or versus an established medicinal product of proven therapeutic value; any other design shall be justified. The treatment of the control groups will vary from case to case and also will depend on ethical considerations and therapeutic area; thus it may, in some instances, be more pertinent to compare the efficacy of a new medicinal product with that of an established medicinal product of proven (established) therapeutic value rather than with the effect of a placebo.

As far as possible, and particularly in trials where the effect of the product cannot be objectively measured, steps shall be taken to avoid bias, including methods of randomization and blinding.

The protocol of the trial must include a thorough description of the statistical methods to be employed, the number and reasons for inclusion of patients (including calculations of the power of the trial), the level of significance to be used and a description of the statistical unit. Measures

taken to avoid bias, particularly methods of randomization, shall be appropriately justified and documented. Inclusion of a large number of subjects in a trial must not be regarded as an adequate substitute for a properly controlled trial.

The safety data shall be reviewed taking into account guidelines published by the Commission, with particular attention to events resulting in changes of dose or need for concomitant medication, serious adverse events, events resulting in withdrawal, and deaths. Any patients or patient groups at increased risk shall be identified and particular attention paid to potentially vulnerable patients who may be present in small numbers, e.g., children, pregnant women, frail elderly, people with marked abnormalities of metabolism or excretion etc. The implication of the safety evaluation for the possible uses of the medicinal product shall be described.

5.3.5.2. Study reports of uncontrolled clinical studies reports of analyses of data from more than one study and other clinical study reports

These reports shall be provided.

5.3.6. Reports of post-marketing experience

If the medicinal product is already authorized in third countries, information shall be given in respect of adverse reactions of the medicinal product concerned and medicinal products containing the same active substance(s), in relation to the usage rates if possible.

5.3.7. Case reports forms and individual patient listings

Case report forms and individual patient data listings shall be provided in the marketing authorization application dossier and presented in the same order as the clinical study reports and indexed by study while securing patient confidential information.

The marketing authorization application dossier shall also be accompanied with laboratory and special observations and statistical analyses of study data.

II. SPECIFIC REQUIREMENTS FOR MODULES OF MARKETING AUTHORIZATION APPLICATION DOSSIERS

6. Requirements for marketing authorization application dossier of generic medicinal products

a) Applications for essentially similar (generic) medicinal products shall be submitted in accordance with this section and taking into account the Rules of performing bioequivalence studies of medicinal products in the Eurasian Economic Union subject to approval by the Commission.

The choice of the reference product for bioequivalence studies shall be made in accordance with the Rules of performing bioequivalence studies of medicinal products in the Eurasian Economic Union subject to approval by the Commission.

Bioequivalence of a generic medicinal product with the original medicinal product shall be demonstrated by appropriate bioavailability studies in accordance with the Rules of performing bioequivalence studies of medicinal products in the Eurasian Economic Union subject to approval by the Commission.

The summary of product characteristics and medication guide of a generic medicinal product shall correspond to the summary of product characteristics and medication guide of the original medicinal product. Where additional therapeutic indications, posology or routes of administrations are claimed in the medication guide of the generic medicinal product in comparison with that of original medicinal product, appropriate clinical data shall be provided.

6.1. Module 1

Applicant shall provide in Module 1.8.2 a concise document (up to 5 pages), summarizing the grounds and evidence used for demonstrating that the medicinal product for which an application is submitted, is a ‘generic’ of a reference medicinal product. This summary should include details on the medicinal product, its qualitative and quantitative composition in active substance(s), its pharmaceutical form and its safety/efficacy profile of the active substance(s) in comparison to the active substance(s) of the reference medicinal product, as well as details related to the bio-availability and bio-equivalence, where necessary, of the medicinal product concerned.

In specific cases, Risk Management Plan might be necessary.

When certain elements are not included, a justification for its absence should be provided in the respective section of the marketing authorization application dossier.

6.2. Module 2

The non-clinical and clinical overviews should particularly focus on the following elements:

- A summary of impurities present in batches of the active substance(s) (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed;
- An evaluation of the bioequivalence studies or a justification why studies were not performed;
- An update of published literature relevant to the substance and the present application. It may be acceptable for articles in "peer review" journals to be annotated for this purpose;
- Every claim in the Summary of Product Characteristics (SPC) not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non-clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies;
- When different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the active substance of the reference medicinal product are used, additional information providing proof that their safety and/or efficacy profile is not different from the one of the reference medicinal product should be submitted.

6.3. Module 3

A complete Module 3 should be submitted.

6.4. Module 4 and Module 5

The results of the bioequivalence studies performed where appropriate shall be included in section 5.3.1. Equivalence demonstration data for biowaiver shall be included in section 5.3.1.2. Method validation report shall also be submitted. Concentration, pharmacokinetics, and statistical data shall also be provided.

Investigator’s details including employer, study site and study dates shall be provided in a bioequivalence study report. Audit certificates shall be attached to the report, where available.

In a bioequivalence study report or separate letter, justification for reference product choice shall be provided in accordance the Rules of performing bioequivalence studies of medicinal products in the Eurasian Economic Union subject to approval by the Commission. Following reference product information shall also be submitted:

- Brand name;
- Strength;
- Dosagel form;
- Marketing authorization holder;
- Date of marketing authorization;
- Certificate of a marketing authorization number;
- Member State where the reference product is authorized for marketing;
- Batch number;
- Manufacturer’s name
- Shelf life;
- Country where the product has been purchased.

The recommendation of the Expert Committee for Medicinal Products on the reference product choice shall be submitted, where available.

The name and composition of test product, batch size, date of manufacture, and where available expiry data shall be provided.

In an annex to the study report, certificates of analysis of the reference product and test product used in the bioequivalence study shall be included.

An official letter signed by the qualified person on quality and declaring that the quantitative composition and manufacturing process of a test product identical to the quantitative composition and manufacturing process of the product to be marketed.

When different chemical forms (salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives) of the active substance of the reference medicinal product are used, additional information providing proof that their safety and/or efficacy profile is not different from the one of the reference medicinal product should be submitted following the Common Technical Document structure.

Non-clinical and clinical data on generic medicinal product generated where necessary shall be included in the appropriate sections of Module 4 and Module 5.

Bioavailability studies shall be conducted where a generic medicinal product fulfils criteria provided in the Rules of performing bioequivalence studies of medicinal products in the Eurasian Economic Union subject to approval by the Commission.

Where the active substance of an essentially similar medicinal product contains the same therapeutic moiety as the authorized product associated with a different salt/ester complex/derivative, additional data (bibliographic overview) or non-clinical and/or clinical data (bioavailability data) demonstrating that there is no change in the pharmacokinetics, pharmacodynamics and/or in toxicity shall be provided. Should this not be the case, this association shall be considered as a new active substance.

7. Requirements for marketing authorization application dossier of hybrid medicinal products

Applications for hybrid medicinal products shall include additional non-clinical and clinical data in accordance with this section.

7.1. Module 1

Applicant shall provide in Module 1.8.2 a concise document (up to 5 pages), summarizing the grounds and evidence used for demonstrating that the medicinal product for which an application is submitted, is a ‘hybrid’ of a reference medicinal product. This summary should include details on the medicinal product, its active substance, pharmaceutical form, strengths, therapeutic indications, route of administration as appropriate in comparison to the reference medicinal product, as well as details related to the bio-availability and bio-equivalence, where necessary, of the medicinal product concerned.

In specific cases, Risk Management Plan might be necessary.

When certain elements are not included, a justification for its absence should be provided in the respective section of the marketing authorization application dossier.

7.2. Module 2

The non-clinical and clinical overviews should particularly focus on the following elements:

- A summary of impurities present in batches of the active substance(s) (and where relevant decomposition products arising during storage) as proposed for use in the product to be marketed;
- An update of published literature relevant to the substance and the present application. It may be acceptable for articles in "peer review" journals to be annotated for this purpose;
- Every claim in the Summary of Product Characteristics (SPC) not known from or inferred from the properties of the medicinal product and/or its therapeutic group should be discussed in the non-clinical/clinical overviews/summaries and substantiated by published literature and/or additional studies;
- When different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the active substance of the reference medicinal product are used, additional information providing proof that their safety and/or efficacy profile is not different from the one of the reference medicinal product should be submitted.

7.3. Module 3

A complete Module 3 should be submitted.

7.4. Module 4 and Module 5

The results of the additional non-clinical and/or clinical studies of the hybrid medicinal product shall be included in appropriate sections of Module 4 or Module 5.

Procedure for conducting additional studies necessary for generic or hybrid medicinal products

Product or application characteristics	Additional data usually required
different salt/ester complex/derivative (with the same therapeutic moiety)	Evidence that there is no change in the pharmacokinetics of the moiety, pharmacodynamics and/or in toxicity which could significantly change the safety/efficacy profile (otherwise, to be considered as a new active substance)
different route/dosage form: new route of administration (for parenteral administration, it is necessary to distinguish between intraarterial, intravenous, intramuscular, subcutaneous and other routes) new dosage form (same route)	Clinical data (safety/efficacy), pharmacokinetics, pre-clinical (e.g. local toxicology), if justified
different strength same route/ dosage form and posology	Bioavailability data in accordance with the Rules of performing bioequivalence studies of medicinal products in the Eurasian Economic Union subject to approval by the Commission suprabioavailable products
same dosage intervals but reduced doses intended to achieve same plasma/blood concentrations as a function of time	Bioavailability studies in accordance with the Rules of performing bioequivalence studies of medicinal products in the Eurasian Economic Union subject to approval by the Commission may suffice

8. Requirements for marketing authorization application dossiers of medicinal products with well-established medicinal use

For medicinal products with recognized therapeutic efficacy and acceptable level of safety (which include, for example, such medicinal products of natural origin as birch bark oil, snake venom, beekeeping products, medicinal leeches, bile, minerals, etc., active substance of which has well established medical use; vitamins and vitamins plus minerals, as well as medicinal products pharmacologic activity of which is defined by biologically active substances of natural origin, antiseptic solutions (hydrogen peroxide, iodine, brilliant green, etc.), water for injection, adsorbents (activated charcoal etc.), appetizer medicinal products, irritant and coating medicinal products) the following specific rules shall apply.

The applicant shall submit Modules 1, 2 and 3 as described in part I of these Requirements.

For Modules 4 and 5, a detailed scientific bibliography shall address non-clinical and clinical characteristics.

The following specific rules shall apply in order to demonstrate the well-established medicinal use:

a) Factors which have to be taken into account in order to establish a well-established medicinal use of constituents of medicinal products are:

- the time over which an active substance has been used,
- quantitative aspects of the use of the substance,

- the degree of scientific interest in the use of the active substance for the previous five years beginning with the day the application for granting a marketing authorization is submitted (reflected in the published scientific literature),

- the coherence of scientific assessments.

Therefore different periods of time may be necessary for establishing well-established use of different substances. The period of time required for establishing a well established medicinal use of a constituent of a medicinal product must not be less than one decade from the first documented use of that substance as a medicinal product within at least 3 Member States. Biologic medicinal products and medicinal products which necessitate conducting bioequivalence and/or clinical studies do not fall under the definition of well-established use medicinal products.

b) The documentation submitted by the applicant should cover all aspects of the safety and efficacy assessment and must include or refer to a review of the relevant literature, taking into account pre- and post-marketing studies and published scientific literature concerning experience in the form of epidemiological studies and in particular of comparative epidemiological studies. All documentation, both favorable and unfavorable, must be communicated. Bibliographic reference to other sources of evidence (post marketing studies, epidemiological studies, etc.), excluding data related to quality control tests may serve as a valid proof of safety and efficacy of a product if an application explains and justifies the use of these sources of information satisfactorily.

c) Particular attention must be paid to any missing information and justification must be given why demonstration of an acceptable level of safety and/or efficacy can be supported although some studies are lacking.

d) The non-clinical and/or clinical overviews contained in Module 2 must explain the relevance of any data submitted which concern a product different from the product intended for marketing. A judgement must be made whether the product studied can be considered as similar to the product, for which application for a marketing authorization has been made in spite of the existing differences.

e) Post-marketing experience with other products containing the same active substances is of particular importance and applicants should put a special emphasis on this issue.

f) where a medicinal product has been marketed in third countries, a periodic safety update report for previous 5 years before the application is submitted shall be provided.

9. Requirements for marketing authorization application dossier of fixed combination medicinal products

For new medicinal products that are a combination of at least 2 known active substances within one pharmaceutical dosage form (i.e. the active substances of a combination medicinal product used in the composition of single-component authorized products), the full dossier (Modules 1 to 5) shall be provided as laid down in Part I of these Requirements. Module 3 shall include information on manufacturing, quality control, and manufacturer of each active substance used in combination medicinal products; co-packaged single-component medicinal products shall not fall under definition of combination medicinal products. In Modules 4 and 5, non-clinical and clinical data on combinations of active substances applied for a marketing authorization shall be provided.

10. Requirements for marketing authorization application dossier of a similar biological medicinal product

For marketing authorization of a biosimilar medicinal product, data on comparability exercise using the reference biological medicinal product shall be submitted. The biosimilar product quality, safety, efficacy, and immunogenicity during manufacturing, non-clinical, and clinical development stages shall be compared to the same reference biological medicinal product in accordance with the Rules of conducting studies of biological medicinal products in the Eurasian Economic Union subject to approval by the Eurasian Economic Commission. An application for a biosimilar medicinal product shall be submitted in accordance with this section.

10.1. Module 1

10.1.1. Applicants should provide in Module 1.8.2, a document, summarizing the grounds and evidence used for demonstrating that the medicinal product for which an application is submitted is: a similar biological medicinal product to a original medicinal product. This summary should include details on the similar biological medicinal product, its active substance, pharmaceutical form, strengths, therapeutic indications, and posology as appropriate in comparison to the original medicinal product.

10.1.2. In Module 10.1 in addition to concise information on marketing authorization holder's pharmacovigilance system, the Risk Management Plan for a biosimilar medicinal product applied for marketing authorization.

10.1.3. When certain elements are not included, a justification for its absence should be provided in the respective section of this Module.

10.2. Module 2

In the Quality Overall Summary, Non-clinical Overview and Clinical Overview, additional comparability data on an applied medicinal product and the reference medicinal product shall be provided together with the criteria for the reference product selection.

In a study report or separate letter, justification for reference product choice shall be provided in accordance the Rules of conducting studies of biological medicinal products in the Eurasian Economic Union subject to approval by the Commission. Following reference product information shall also be submitted:

- Brand name;
- Strength and dosage form;
- Marketing authorization holder;
- Date of marketing authorization and certificate of a marketing authorization number;
- Member States where the reference product is authorized for marketing;
- Batch number of the reference product used in studies and pharmaceutical development;
- Manufacturer's name
- Shelf life;
- Country where the product has been purchased.

The recommendation of the Expert Committee for Medicinal Products on the reference product choice shall be submitted, where available.

The name and composition of test product(s), batch size, date of manufacture, and where available expiry data shall be provided.

The extent of generated non-clinical and/clinical data shall be provided in accordance with the Rules of conducting studies of biological medicinal products in the Eurasian Economic Union subject to approval by the Commission. In an annex to the study report, certificates of analysis of the reference product and test product used in the study shall be included.

10.3. Module 3

Module 3 shall additionally include following data taking into account the Rules of conducting studies of biological medicinal products in the Eurasian Economic Union subject to approval by the Commission:

a) Demonstration of molecular and biological similarity between the biosimilar medicinal product active substance and reference biological medicinal product active substance in terms of the primary structure and higher order structures, post-translational modifications including, in particular glycoforms, potency, purity, and impurities;

b) Demonstration of pharmaceutical similarity in terms of pharmaceutical form, qualitative and quantitative composition, strength, posology, storage conditions, shelf life, stability, and impurity profile between the biosimilar and reference medicinal product;

c) In case of any differences in impurities or excipients, possible influence of these on clinical safety and efficacy profile shall be evaluated and acceptability of such differences shall be provided using experimental data and literature references; where clinical relevance of observed

differences is unknown, in particular in terms of safety, additional pre- and post-marketing studies shall be conducted;

d) Complete description and data on the manufacturing process from expression construct, original cell clone, and cell bank development, cell culture, harvesting, purification, additional manufacturing steps after extraction and purification of the product, filling for the bulk product and finished product to storage;

e) testing conducted in the course of pharmaceutical development of biosimilar medicinal products to characterize and justify its pharmaceutical form, composition and container/closure system, including its integrity to prevent microbiological contamination;

f) the biosimilar medicinal product specification which shall include important finished product quality attributes set for reference biological medicinal product, such as identity, purity, potency, size and charge heterogeneity, hydrophobicity (where appropriate), sialylation level, number of separate polypeptide chains, functional site glycosylation, aggregation, the following impurities: host cell proteins and DNA, etc.

g) Stability data.

10.4. Module 4

Module 4 shall include non-clinical comparability data on the biosimilar medicinal product and reference medicinal product in accordance with the Rules of conducting studies of biological medicinal products in the Eurasian Economic Union subject to approval by the Commission.

10.5. Module 5

In accordance with the Rules of conducting studies of biological medicinal products in the Eurasian Economic Union subject to approval by the Commission, Module 5 shall include documents and particulars containing:

a) Clinical data on the biosimilar medicinal product in comparison with the reference medicinal product including:

- Pharmacokinetics data; single dose pharmacokinetics studies, multiple dose pharmacokinetics studies (where dose response relationship observed);
- Comparison of pharmacokinetic data of biosimilar medicinal product to that of the reference product shall include investigation of absorption, bioavailability, elimination characteristics (i.e. clearance and/or half-life), pharmacodynamic data; pharmacodynamic response shall be evaluated in the appropriate population using doses within the steep part of the dose response curve according to non-clinical data; selection of pharmacodynamic markers shall be guided by the clinical relevance thereof;
- Comparative clinical data including evaluation of adverse event/reaction type, frequency, and severity; immunogenicity testing in the target population (comparison of frequency and type of the antibodies, possible consequence of immune response for the biosimilar medicinal product and reference product); immunogenicity testing shall be conducted in the patient population having the highest risk of immunological response and immunological adverse reactions;
- Justification of the antibody assay strategy including method selection, evaluation, and characterization, sampling time determination (including pre-dose sample), sample volume, processing, and storage, as well as statistical analysis methods; antibody assay test procedures shall be validated for the intended use; preliminary analysis of adequate method sensitivity shall be performed; neutralizing antibodies measurement shall be envisaged;
- Follow-up period in immunogenicity testing; this period shall correspond to the proposed treatment period and expected antibody formation time; unless otherwise justified, at least one-year follow-up period shall be envisaged;
- Clinically significant episodes of antibody formation and persistence within a specific time period; in this case, changes in the immune response profile and its clinical consequences shall be investigated pre- and post-marketing;
- it is recommended to generate the clinical data required for the biosimilar comparability exercise with the biosimilar product derived from the commercial manufacturing process and therefore representing the quality profile of the batches to become commercialized; any

deviation from this recommendation should be justified and supported by adequate additional bridging data between final product and non-final product in accordance with the Rules of conducting studies of biological medicinal products in the Eurasian Economic Union subject to approval by the Commission;

b) Risk Management Plan together with the Safety Specification including important observed and potential safety concerns of the reference product, product class and/or biosimilar product) and biosimilar medicinal product Pharmacovigilance Plan for post-marketing period including proposed post-authorization measures and risk minimization measures based on the Safety Specification together with information for patients and/or healthcare providers and pharmacists.

11. Documentation for applications for a marketing authorization envisaging imposing post marketing measures (conditional marketing authorization)

When the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use, because:

- the indications for which the product in question is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence,
- in the present state of scientific knowledge, comprehensive information cannot be provided,
- it would be contrary to generally accepted principles of medical ethics to collect such information,
- marketing authorization may be granted subject to certain specific obligations.
- These obligations may include the following:
- the applicant shall complete an identified program of studies within a time period specified by the competent authority, the results of which shall form the basis of a reassessment of the benefit-risk profile,
- the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision, possibly in a hospital and in the case of a radiopharmaceutical, by an authorized person,
- the medication guide, SmPC and any medical information shall draw the attention of the medical practitioner to the fact that the particulars available concerning the medicinal product in question are as yet inadequate in certain specified respects.

III. REQUIREMENTS FOR MARKETING AUTHORIZATION APPLICATION DOSSIER DOCUMENTS OF PARTICULAR TYPES OF MEDICINAL PRODUCTS

12. Biological medicinal products

This Part lays down specific requirements for drawing up Module 3 of vaccines, blood products related to the nature of identified medicinal products.

12.1. Plasma-derived medicinal product

For medicinal products derived from human blood or plasma and by derogation from the provisions of Module 3 of Part I of these Requirements, the dossier requirements mentioned in ‘Information related to the starting and raw materials’, for starting materials made of human blood/plasma may be replaced by a Plasma Master File certified in accordance with this Part.

12.1.1. General Principles of Drawing up of Marketing Authorization Application Dossier

For the purposes of these Requirements:

- Plasma Master File shall mean a stand-alone documentation, which is separate from the dossier for marketing authorization which provides all relevant detailed information on the characteristics of the entire human plasma used as a starting material and/or a raw material for the manufacture of sub/intermediate fractions, constituents of the excipient and active substance(s), which are part of medicinal products or medical devices.

- Every center or establishment for fractionation/processing of human plasma shall prepare and keep updated the set of detailed relevant information referred to in the Plasma Master File.
- The Plasma Master File shall be submitted to the competent authority of the Member State by the applicant for a marketing authorization or the holder of the marketing authorization. Where the applicant for a marketing authorization or the marketing authorization holder differs from the holder of the Plasma Master File, the Plasma Master File shall be made available to the applicant or marketing authorization holder for submission to the competent authority. In any case, the applicant or marketing authorization holder shall take responsibility for the medicinal product.
- Any marketing authorization dossier containing a human plasma-derived constituent shall refer to the Plasma Master File corresponding to the plasma used as a starting/raw material.

12.1.2. Additional requirements for dossier content

the Plasma Master File shall include information on the plasma used as starting/raw material, in particular:

- Plasma origin:
- information on centers or establishments in which blood/plasma collection is carried out, including inspection and approval, and epidemiological data on blood transmissible infections.
- information on centers or establishments in which testing of donations and plasma pools is carried out, including inspection and approval status.
- selection/exclusion criteria for blood/plasma donors.
- system in place which enables the path taken by each donation to be traced from the blood/plasma collection establishment through to finished products and vice versa.
- Plasma quality and safety:
- compliance with monographs of the Pharmacopoeia of the Eurasian Economic Union or, in the absence thereof, pharmacopoeias of the Member Stats or main pharmacopeias in accordance with the Eurasian Economic Union Member States Pharmacopeia Harmonization Conception.
- testing of blood/plasma donations and pools for infectious agents, including information on test methods and, in the case of plasma pools, validation data on the tests used.
- technical characteristics of bags for blood and plasma collection, including information on anticoagulants solutions used.
- conditions of storage and transport of plasma.
- procedures for any inventory hold and/or quarantine period.
- characterization of the plasma pool.
- System in place between the plasma-derived medicinal product manufacturer and/or plasma fractionator/processor on the one hand, and blood/plasma collection and testing centers or establishments on the other hand, which defines the conditions of their interaction and their agreed specifications.

In addition, the Plasma Master File shall provide a list of the medicinal products for which the Plasma Master File is valid, whether the medicinal products have been granted a marketing authorization or are in the process of being granted such an authorization, or these medicinal products are under clinical development.

12.1.3. Assessment of the marketing authorization application dossier and Certification

For medicinal products not yet authorized, the marketing authorization applicant shall submit a full dossier to a competent authority of the Member State, which shall be accompanied by a separate Plasma Master File where one does not already exist.

The Plasma Master File is subject to a scientific and technical evaluation within granting a marketing authorization for a medicinal product and assessment thereof. A positive evaluation shall result in a certificate of compliance with Union legislation for the Plasma Master File, which shall be accompanied by the evaluation report. The certificate issued shall apply throughout the Union.

The Plasma Master File shall be updated and re-certified on an annual basis.

Changes subsequently introduced to the terms of a Plasma Master File must follow evaluation in accordance with variation procedure.

The competent authorities of the Member States that will grant or has granted the marketing authorization (renewal of the marketing authorization, variation to the marketing authorization) shall take into account the certification, re-certification or variation of the Plasma Master File on the concerned medicinal products.

12.2. Vaccines

For vaccines for human use and by derogation from the provisions of Module 3 on 'Active substance(s)', the following requirements when based on the use of a Vaccine Antigen Master File system shall apply.

The marketing authorization application dossier of a vaccine other than human influenza vaccine, shall be required to include a Vaccine Antigen Master File for every vaccine antigen that is an active substance of this vaccine.

12.2.1. General principles

Vaccine Antigen Master File shall mean a stand-alone part of the marketing authorisation application dossier for a vaccine, which contains all relevant information of biological, pharmaceutical and chemical nature concerning each of the active substances, which are part of this medicinal product. The stand-alone part may be common to one or more monovalent and/or combined vaccines presented by the same applicant or marketing authorization holder.

A vaccine may contain one or several distinct vaccine antigens. There are as many active substance(s) as vaccine antigen(s) present in a vaccine.

A combined (polyvalent) vaccine contains at least two distinct vaccine antigens aimed at preventing a single or several infectious diseases.

A monovalent vaccine is a vaccine, which contains one vaccine antigen aimed at preventing a single infectious disease.

12.2.2. Additional requirements for marketing authorization application dossier content

The Vaccine Antigen Master File shall contain the following information extracted from the relevant part (Active substance) of Module 3 on 'Quality Data' as delineated in Part I of these Appendix:

Active Substance

1. General Information, including compliance with the relevant monograph(s) of the Pharmacopoeia of the Eurasian Economic Union or, in the absence thereof, pharmacopoeias of the Member Stats or main pharmacopeias in accordance with the Eurasian Economic Union Member States Pharmacopeia Harmonization Conception.

2. Information on the manufacture of the active substance: this heading must cover the manufacturing process, information on the starting and raw materials, specific measures on transmissible spongiform encephalopathies and adventitious agents safety evaluation and facilities and equipment.

3. Characterization of the active substance

4. Quality control of the active substance

5. Reference standard and materials

6. Container and closure system of the active substance

7. Stability of the active substance.

8. Assessment and Conclusion

For novel vaccines, which contain a novel vaccine antigen, the applicant shall submit to a competent authority a full marketing authorization application dossier including all the Vaccine Antigen Master Files corresponding to each single vaccine antigen that is part of the novel vaccine where no master file already exists for the single vaccine antigen. A positive evaluation shall result in a certificate of compliance to the Union legislation for each Vaccine Antigen Master File, which shall be accompanied by the evaluation report. The certificate shall apply throughout the Union.

The provisions of the first indent shall also apply to every vaccine, which consists of a novel combination of vaccine antigens, irrespective of whether or not one or more of these vaccine antigens are part of vaccines already authorized in the Member States.

Changes to the content of a Vaccine Antigen Master File shall be subject to an evaluation in accordance with variation procedure. The competent authorities of the Member States that will grant or has granted the marketing authorization (renewal of the marketing authorization, variation to the marketing authorization) shall take into account the certification, re-certification or variation of the Plasma Master File on the concerned medicinal products.

12.3. Simplified marketing authorization application dossier of vaccines in well-established medical use which had been manufactured within Member States before 2000

For vaccines vaccine antigen of which is in well-established use with recognized efficacy and acceptable level of safety which had been manufactured within Member States before 2000, the following rules apply.

An applicant shall provide Module 3 drawn up as laid down in Part I and section 12.2 of Part II of these Appendix.

In module 4 and 5, in place of non-clinical and clinical reports scientific bibliography shall be provided which shall contain non-clinical and clinical characteristics of a vaccine.

13. Radiopharmaceuticals and precursors

The application dossier for marketing authorization for a radiopharmaceuticals and precursors thereof shall be drawn up as laid down in this section.

13.1. Radiopharmaceuticals

13.1.1. Module 3

In the context of a radiopharmaceutical kit, which is to be radio-labelled after supply by the manufacturer, the ‘active substance’ is considered to be that part of the formulation which is intended to carry or bind the radionuclide. The description of the manufacturing method of radiopharmaceutical kits shall include details of the manufacture of the kit and details of its recommended final processing to produce the radioactive medicinal product. The necessary specifications of the radionuclide shall be described in accordance, where relevant, with the general monograph or specific monographs of the Pharmacopoeia of the Eurasian Economic Union or, in the absence thereof, pharmacopoeias of the Member Stats or main pharmacopeias in accordance with the Eurasian Economic Union Member States Pharmacopeia Harmonization Conception.

In addition, any compounds essential for the radio-labelling shall be described. The structure of the radio-labelled compound shall also be described.

For radionuclides, the nuclear reactions involved shall be discussed.

In a generator, both mother and daughter radionuclides shall be considered as active substances.

Details of the nature of the radio-nuclide, the identity of the isotope, likely impurities, the carrier, the use and the specific activity shall be provided.

Starting materials include irradiation target materials.

Considerations on chemical/radiochemical purity and its relationship to biodistribution shall be provided.

Radionuclide purity, radiochemical purity and specific activity shall be described.

For generators, details on the testing for mother and daughter radionuclides are required. For generator-eluates, tests for mother radionuclides and for other constituents of the generator system shall be provided.

The requirement to express the content of active substances in terms of the mass of active entities shall only apply to radio-pharmaceutical kits. For radionuclides, radioactivity shall be expressed in Becquerels at a given date and, if necessary, time with reference to time zone. The type of radiation shall be indicated.

For kits, the specifications of the finished product shall include tests on performance of products after radio-labelling. Appropriate controls on radiochemical and radionuclidic purity of the radio-labelled compound shall be included. Any material essential for radio-labelling shall be identified and assayed.

Information on stability shall be given for radionuclide generators, radio-nuclide kits and radio-labelled products. The stability during use of radio-pharmaceuticals in multi-dose vials shall be documented.

13.1.2. Module 4

It is appreciated that toxicity may be associated with a radiation dose. In diagnosis, this is a consequence of the use of radio-pharmaceuticals; in therapy, it is the property desired. The evaluation of safety and efficacy of radio-pharmaceuticals shall, therefore, address requirements for medicinal products and radiation dosimetry aspects. Organ/tissue exposure to radiation shall be documented. Absorbed radiation dose estimates shall be calculated according to a specified, internationally recognized system by a particular route of administration.

13.1.3. Module 5

The results of clinical trials shall be provided where applicable otherwise justified in the clinical overviews (Module 2).

13.2. Radio-pharmaceutical precursors for radio-labelling purposes

In the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes, the primary objective shall be to present information which would address the possible consequences of poor radio-labeling efficiency or in vivo dissociation of the radio-labeled conjugate, i.e. questions related to the effects produced in the patient by free radio-nuclide. In addition, it is also necessary to present relevant information relating to occupational hazards, i.e. radiation exposure to hospital staff and to the environment.

In particular, the following information where applicable shall be provided:

13.2.1. Module 3

The provisions of Module 3 shall apply to the registration of radio-pharmaceutical precursors as define above (indents a) to i)), where applicable.

13.2.2. Module 4

Concerning single dose and repeat dose toxicity, the results of studies carried out in conformity with the provisions related to the Rules of the Good Laboratory Practice subject to approval by Commission, unless otherwise justified.

Mutagenicity studies on the radio-nuclide are not considered to be useful in this particular case.

Information relating to the chemical toxicity and disposition of the relevant ‘cold’ nuclide shall be presented.

13.2.3. Module 5

Clinical information generated from clinical studies using on the precursor itself is not considered to be relevant in the specific case of a radio-pharmaceutical precursor intended solely for radio-labelling purposes.

However, information demonstrating the clinical utility of the radio-pharmaceutical precursor when attached to relevant carrier molecules shall be presented.

14. Homeopathic medicinal products

14.1. Module 3

Terminology

The Latin name of the homeopathic stock (homeopathic active substance) described in the marketing authorization application dossier must be in accordance with the Latin title of the Pharmacopoeia of the Eurasian Economic Union (where available) or by a homeopathic pharmacopoeia of Member States or the Homeopathic pharmacopoeia of Germany, the Pharmacopoeia of France and the European Pharmacopoeia.

Control of starting materials

The particulars and documents on the quality of all product components including the homeopathic stock and excipients shall be supplemented in accordance with requirements as laid down in the ‘Composition’ section of monographs and normative documents. For homeopathic stock, those are monographs of Pharmacopoeia of the Eurasian Economic Union (where available) or by a homeopathic pharmacopoeia of Member States or the Homeopathic pharmacopoeia of

Germany, the Pharmacopoeia of France and the European Pharmacopoeia; for excipients, those are normative documents and monographs of the abovementioned pharmacopoeias.

The general quality requirements shall apply to all of the starting and raw materials as well as intermediate steps of the manufacturing process up to the final dilution to be incorporated into the finished medicinal product. Where the homeopathic stock contains highly potent or toxic active substance, the content of that substance shall be assayed using appropriate test method and appropriate acceptance criteria established, e.g. two-side test for the content of such a substance or testing D4 dilution. In general, such an evaluation is not needed where dilutions are higher than D4 or in case of D100 dilutions.

In case dilutions are involved, these dilution steps should be done in accordance with the homeopathic manufacturing methods laid down in the relevant monograph of the Pharmacopoeia of the Eurasian Economic Union (where available) or by a homeopathic pharmacopoeia of Member States or the Homeopathic pharmacopoeia of Germany, the Pharmacopoeia of France and the European Pharmacopoeia; the scale and the dilution shall be specified.

Control tests on the finished medicinal product

The general quality requirements shall apply to the homeopathic finished medicinal products, any exception needs to be duly justified by the applicant.

Identification and assay of all the toxicologically relevant homeopathic stock shall be carried out where highly potent or toxic homeopathic stock is used in manufacturing process of the finished homeopathic product.

If it can be justified that an identification and/or an assay on all the toxicologically relevant constituents is not possible e.g. due to their dilution in the finished medicinal product the quality shall be demonstrated by complete validation of the manufacturing and dilution process.

Identification and assay of all the relevant homeopathic stocks shall be carried out where highly potent or toxic homeopathic stock is not used in manufacturing process of the finished homeopathic product in accordance with monographs on particular homeopathic stocks, where necessary.

Stability tests

The stability of the finished medicinal product must be demonstrated. Stability data from the homeopathic stocks are generally transferable to dilutions/triturations obtained thereof. If no identification or assay of the active substance is possible due to the degree of dilution, stability data of the pharmaceutical form may be considered.

14.2. Module 4

Non-clinical toxicity data

Any missing information must be justified, e.g., justification must be given why demonstration of an acceptable level of safety can be supported although some studies are lacking.

For new homeopathic products (matrix solutions, triturations, and other components) not described in pharmacopoeias and monographs, non-clinical toxicity data, dose response data, and subsequent clinical data are essential.

14.3. Module 5

Post-marketing clinical data, where available.

Any missing data shall be justified, e.g. to demonstrate acceptable efficacy and safety profile in the absence of particular studies.

For new homeopathic medicinal products (matrix solutions, triturations, and other components) not described in pharmacopoeias and monographs, clinical data (in accordance with requirements of this Appendix) and dose response data are essential.

For new homeopathic medicinal products having longstanding use and described in pharmacopoeias, the scientific review of the efficacy and safety of homeopathic medicinal product in the claimed area shall be supplemented.

In summary of product characteristics and medication guide, the statement ‘homeopathic medicinal product’ shall be included.

14.4. Simplified registration dossier for the homeopathic medicinal products

For homeopathic medicinal products, simplified registration dossier may be supplemented where the following conditions are satisfied:

- medicinal product is administered orally or externally, locally, in the form of inhalation;
- no specific therapeutic indication appears on the packaging, SmPC or medication guide of the medicinal product;
- there is a sufficient degree of dilution to guarantee the safety of the medicinal product; in particular, the medicinal product may not contain either more than one part per 10 000 of the mother tincture or more than 1/100th of the smallest dose used in allopathy with regard to active substances whose presence in an allopathic medicinal product results in the obligation to submit a doctor's prescription.

For such homeopathic medicinal products, demonstration of the therapeutic efficacy is not needed. Classification of such homeopathic medicinal products shall be determined in the course of granting a marketing authorization.

An application for special, simplified registration may cover a series of medicinal products derived from the same homeopathic stock or stocks (of animal, mineral, or herbal origin).

The following documents shall be included with the application in order to demonstrate, in particular, the pharmaceutical quality and the batch-to-batch homogeneity of the products concerned:

- scientific name or other name given in a pharmacopoeia of the homeopathic stock or stocks, together with a statement of the various routes of administration, pharmaceutical forms and degree of dilution to be registered,
- one or more mock-ups of the outer packaging and of the inner packaging, as well as summary of product characteristics and medication guide (patient leaflet) of homeopathic medicinal products submitted for simplified registration,
- dossier describing how the homeopathic stock or stocks is/are obtained and controlled, and justifying its/their homeopathic use, on the basis of an adequate bibliography,
- manufacturing and control file for each pharmaceutical form and a description of the method of dilution and potentization,
- manufacturing authorization for the medicinal product concerned and a document that confirms compliance with the Rules of the Good Manufacturing Practice of the Union,
- copies of any registrations or authorizations obtained for the same medicinal product in other countries,
- data concerning the stability of the medicinal product.

15. Herbal medicinal products

Applications for herbal medicinal products shall provide a full dossier in which the following specific details shall be included.

15.1. Module 3

The provisions of Module 3 of Section 3, Part I of this Appendix, including compliance with monograph(s) of the Pharmacopoeia of the Eurasian Economic Union or pharmacopoeias of Member States, shall apply to the authorization of herbal medicinal products. The state of scientific knowledge at the time when the application is lodged shall be taken into account.

15.1.1. Herbal substances and herbal preparations

For the purposes of this Appendix the term ‘active substance of herbal origin’ shall include both terms ‘herbal substance’ and ‘herbal preparations’.

With respect to the nomenclature of the herbal substance, the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the origin (wild or cultivated), the parts of the plants, the definition of the herbal substance shall be provided.

With respect to the nomenclature of the herbal preparation prepared from herbal substance (using extraction, distillation, expression, fractionation, purification, concentration, fermentation,

etc.), the binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable), the origin (wild or cultivated), the parts of the plants shall be provided.

To document the section of the structure for herbal substance(s) and herbal preparation(s) where applicable, the physical form, the description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereo-chemistry, the molecular formula, and the relative molecular mass) as well as other constituent(s) shall be provided.

To document the section on the manufacturer of the herbal substance, the name, address, and responsibility of each supplier, including contractors, and each proposed site or facility involved in production/collection and testing of the herbal substance shall be provided, where appropriate.

To document the section on the manufacturer of the herbal preparation, the name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation shall be provided, where appropriate.

With respect to the description of manufacturing process and process controls for the herbal substance, information shall be provided to adequately describe the plant production and plant collection, including the geographical source of the medicinal plant and cultivation, harvesting, drying and storage conditions.

With respect to the description of manufacturing process and process controls for the herbal preparation, information shall be provided to adequately describe the manufacturing process of the herbal preparation, including description of the processing, solvents and reagents, purification stages and standardization.

With respect to the manufacturing process development, a brief summary describing the development of the herbal substance(s) and herbal preparation(s) where applicable shall be provided, taking into consideration the proposed route of administration and usage. Results comparing the phytochemical composition of the herbal substance(s) and herbal preparation(s) where applicable used in supporting bibliographic data and the herbal substance(s) and herbal preparation(s), where applicable, contained as active substance(s) in the herbal medicinal product applied for shall be discussed, where appropriate.

With respect to the elucidation of the structure and other characteristics of the herbal substance, information on the botanical, macroscopical, microscopical, phytochemical characterization, and biological activity if necessary, shall be provided.

With respect to the elucidation of the structure and other characteristics of the herbal preparation, information on the phyto- and physicochemical characterization, and biological activity if necessary, shall be provided.

The specifications for the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

The analytical procedures used for testing the herbal substance(s) and herbal preparation(s) where applicable shall be provided. With respect to the validation of analytical procedures, analytical validation information, including experimental data for the analytical procedures shall be provided.

With respect to batch analyses, description of batches and results of batch analyses for the herbal substance(s) and herbal preparation(s) where applicable shall be provided, including those for pharmacopoeial substances.

Justification for the specifications of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

Information on the reference standards or reference materials used for testing of the herbal substance(s) and herbal preparation(s) where applicable shall be provided.

Where the herbal substance or the herbal preparation is the subject of a monograph of the European Pharmacopoeia, the applicant can apply for a certificate of suitability that was granted by the European Directorate for the Quality of Medicines.

15.1.2. Herbal Medicinal Products

With respect to the formulation development, a brief summary describing the development of the herbal medicinal product should be provided, taking into consideration the proposed route of

administration and usage. Results comparing the phytochemical composition of the products used in supporting bibliographic data and the herbal medicinal product applied for shall be discussed.

With respect to the description of manufacturing process and process controls for the herbal medicinal product, information shall be provided to adequately describe the manufacturing process of the herbal medicinal product, including description of the processing, solvents and reagents, purification stages and standardization.

15.1.3. Modules 4 and 5

Non-clinical (toxicological and pharmacological) and clinical data

For combination herbal products including combinations with vitamins and/or minerals, where particular constituents of a combination insufficiently investigated, data on each constituents shall be provided.

15.2. Simplified marketing authorization application dossier for the herbal medicinal products

A simplified marketing authorization application dossier for herbal medicinal products (in the form of tinctures, extracts, etc. as well as cut, commuted, comminuted or powdered, compressed plant parts and other products) which fulfil the following criteria:

- they have indications appropriate by virtue of their composition and purpose and are intended and designed for use without the supervision of a medical practitioner for diagnostic purposes or for prescription or monitoring of treatment,
- they are exclusively for administration in accordance with a strength and posology specified in summary of product characteristics,
- they are an oral, external and/or inhalation preparation,
- the safety of a herbal medicinal product is based on longstanding experience (for at least ten years from the first systematic and documented use of that herbal medicinal product within at least 3 Member States),
- any labelling and user package leaflet shall contain a statement to the effect that:
- the product is a traditional herbal medicinal product for use in specified indication(s) exclusively based upon longstanding use; and
- the user should consult a doctor or a qualified health care practitioner if the symptoms persist during the use of the medicinal product or if adverse effects not mentioned in the package leaflet occur.

The presence in the herbal medicinal product of vitamins or minerals for the safety of which there is well-documented evidence shall not prevent the product from being eligible for simplified registration, provided that the action of the vitamins or minerals is ancillary to that of the herbal active ingredients regarding the specified claimed indication(s).

15.2.1. Module 2

Bibliographical or expert evidence (who drew up Modules 2.4 and 2.5) to the effect that the medicinal product in question, or a corresponding product has been in medicinal use throughout a period of at least 10 years preceding the date of the application, within the all Member States.

15.2.2 Particulars and documents of a simplified registration dossier

To demonstrate pharmaceutical quality and the batch-to-batch homogeneity of the products, the application shall be accompanied with a registration dossier including Modules 1 to 3 in accordance with Appendix 4 to Rules of authorization and assessment of medicinal products for human use subject to approval by the Commission. Modules 4 and 5 shall be drawn up using copies of bibliographic references on which Modules 2.4 and 2.5 drawn up by experts are based.

16. Orphan medicinal products (products intended to treat rare diseases)

In the case of an orphan medicinal products, general provisions of Part II (exceptional circumstances) can be applied. The applicant shall then justify in the non-clinical and clinical summaries the reasons for which it is not possible to provide the complete information and shall provide a justification of the benefit/risk balance for the orphan medicinal product concerned.

IV. ADVANCED THERAPY MEDICINAL PRODUCTS

17.1. Introduction

Marketing authorization application dossier for advanced therapy medicinal products shall follow the format requirements (Modules 1 to 5) described in Part I of this Appendix.

The technical requirements for Modules 3 to 5 for advanced therapy biological medicinal products, as described in Part I of this Appendix, shall apply. The specific requirements for advanced therapy medicinal products described in sections 17.3, 17.4 and 17.5 of this part explain how the requirements in Part I apply to advanced therapy medicinal products.

Due to the specific nature of advanced therapy medicinal products, a risk-based approach may be applied to determine the extent of quality, non-clinical and clinical data to be included in the marketing authorization application, in accordance with the applicable guidelines of the Union or, in absence thereof, guidelines of the Member States.

The risk analysis may cover the entire development. Risk factors that may be considered include: the origin of the cells (autologous, allogeneic, xenogeneic), the ability to proliferate and/or differentiate and to initiate an immune response, the level of cell manipulation, the combination of cells with bioactive molecules or structural materials, the nature of the gene therapy medicinal products, the extent of replication competence of viruses or micro-organisms used in vivo, the level of integration of nucleic acids sequences or genes into the genome, the long time functionality, the risk of oncogenicity and the mode of administration or use.

Relevant available non-clinical and clinical data or experience with other, related advanced therapy medicinal products may also be considered in the risk analysis.

Any deviation from the requirements of this Appendix shall be scientifically justified in Module 2 of the application dossier. The risk analysis described above, when applied, shall also be included and described in Module 2. In this case, the methodology followed, the nature of the identified risks and the implications of the risk based approach for the development and evaluation program shall be discussed and any deviations from the requirements of this Appendix resulting from the risk analysis shall be described.

17.2. Definitions

17.2.1. Gene therapy medicinal products

Gene therapy medicinal product means a biological medicinal product which has the following characteristics:

it contains an active substance which contains or consists of a recombinant nucleic acid used in or administered to human beings with a view to regulating, repairing, replacing, adding or deleting a genetic sequence;

its therapeutic, prophylactic or diagnostic effect relates directly to the recombinant nucleic acid sequence it contains, or to the product of genetic expression of this sequence.

Gene therapy medicinal products shall not include vaccines against infectious diseases.

17.2.2. Somatic cell therapy medicinal product

Somatic cell therapy medicinal product means a biological medicinal product which has the following characteristics:

contains or consists of cells or tissues that have been subject to substantial manipulation so that biological characteristics, physiological functions or structural properties relevant for the intended clinical use have been altered, or of cells or tissues that are not intended to be used for the same essential function(s) in the recipient and the donor. The following manipulations: cutting, grinding, shaping, centrifugation, soaking in antibiotic or antimicrobial solutions, sterilization, irradiation, cell separation, concentration or purification, filtering, lyophilization, freezing, cryopreservation, vitrification., in particular, shall not be considered as substantial manipulations.

is presented as having properties for, or is used in or administered to human beings with a view to treating, preventing or diagnosing a disease through the pharmacological, immunological or metabolic action of its cells or tissues.

17.3. Specific requirements regarding Module 3

17.3.1. Specific requirements for all advanced therapy medicinal products

A description of the traceability system that the applicant intends to establish and maintain to ensure that the individual product and its starting and raw materials, including all substances coming into contact with the cells or tissues it may contain, can be traced through the sourcing, manufacturing, packaging, storage, transport and delivery to the hospital, institution or private practice where the product is used, shall be provided.

The traceability system shall be complementary to the requirements established by the Members States, as regards human blood cells.

17.3.2. Specific requirements for gene therapy medicinal products

17.3.2.1. Introduction: finished product, active substance and starting materials

17.3.2.1.1. Gene therapy medicinal product containing recombinant nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es)

The finished medicinal product shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es) formulated in their final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device.

The active substance shall consist of nucleic acid sequence(s) or genetically modified microorganism(s) or virus(es).

17.3.2.1.2. Gene therapy medicinal product containing genetically modified cells

The finished medicinal product shall consist of genetically modified cells formulated in the final immediate container for the intended medical use. The finished medicinal product may be combined with a medical device or active implantable medical device.

The active substance shall consist of cells genetically modified by one of the products described in section 17.3.2.1.1 above.

17.3.2.1.3. In the case of products consisting of viruses or viral vectors, the starting materials shall be the components from which the viral vector is obtained, i.e. the master virus vector seed or the plasmids used to transfect the packaging cells and the master cell bank of the packaging cell line.

17.3.2.1.4. In the case of products consisting of plasmids, non-viral vectors and genetically modified microorganism(s) other than viruses or viral vectors, the starting materials shall be the components used to generate the producing cell, i.e. the plasmid, the host bacteria and the master cell bank of recombinant microbial cells.

17.3.2.1.5. In the case of genetically modified cells, the starting materials shall be the components used to obtain the genetically modified cells, i.e. the starting materials to produce the vector, the vector and the human or animal cells. The principles of good manufacturing practice shall apply from the bank system used to produce the vector onwards.

17.3.2.2. Specific requirements

In addition to the requirements set out in sections 17.3.2.1 and 17.3.2.2 of Part I of this Appendix, the following requirements shall apply:

a) information shall be provided on all the starting materials used for the manufacture of the active substance, including the products necessary for the genetic modification of human or animal cells and, as applicable, subsequent culture and preservation of the genetically modified cells (where necessary), taking into consideration the possible absence of purification steps;

b) for products containing a microorganism or a virus, data on the genetic modification, sequence analysis, attenuation of virulence, tropism for specific tissues and cell types, cell cycle dependence of the microorganism or virus, pathogenicity and characteristics of the parental strain shall be provided;

c) process-related impurities and product-related impurities shall be described in the relevant sections of the dossier, and in particular replication competent virus contaminants if the vector is designed to be replication incompetent;

d) for plasmids, quantification of the different plasmid forms shall be undertaken throughout the shelf life of the product;

e) for genetically modified cells, the characteristics of the cells before and after the genetic modification, as well as before and after any subsequent freezing/storage procedures, shall be tested.

For genetically modified cells, in addition to the specific requirements for gene therapy medicinal products, the quality requirements for somatic cell therapy medicinal products and tissue engineered products (see section 17.3.3 of these Requirements) shall apply.

17.3.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products

17.3.3.1. Introduction: finished product, active substance and starting materials

The finished medicinal product shall consist of the active substance formulated in its immediate container for the intended medical use, and in its final combination for combined advanced therapy medicinal products.

The active substance shall be composed of the engineered cells and/or tissues.

Additional substances (e.g. scaffolds, matrices, devices, biomaterials, biomolecules and/or other components) which are combined with manipulated cells of which they form an integral part shall be considered as starting materials, even if not of biological origin.

Materials used during the manufacture of the active substance (e.g. culture media, growth factors) and that are not intended to form part of the active substance shall be considered as raw materials.

17.3.3.2. Specific requirements

In addition to the requirements set out in sections 17.3.2.1 and 17.3.2.2 of Part I of this Appendix, the following requirements shall apply:

17.3.3.2.1. Starting materials

Summary information shall be provided on donation, procurement and testing of the human tissue and cells used as starting materials. If non-healthy cells or tissues (e.g. cancer tissue) are used as starting materials, their use shall be justified.

If allogeneic cell populations are being pooled, the pooling strategies and measures to ensure traceability shall be described.

The potential variability introduced through the human or animal tissues and cells shall be addressed as part of the validation of the manufacturing process, characterization of the active substance and the finished product, development of assays, setting of specifications and stability.

For xenogeneic cell-based products, information on the source of animals (such as geographical origin, animal husbandry, age), specific acceptance criteria, measures to prevent and monitor infections in the source/donor animals, testing of the animals for infectious agents, including vertically transmitted micro-organisms and viruses, and evidence of the suitability of the animal facilities shall be provided.

For cell-based products derived from genetically modified animals, the specific characteristics of the cells related to the genetic modification shall be described. A detailed description of the method of creation and the characterization of the transgenic animal shall be provided.

For the genetic modification of the cells, the technical requirements specified in section 17.3.2 shall apply.

The testing regimen of any additional substance (scaffolds, matrices, devices, biomaterials, biomolecules or other components), which are combined with engineered cells of which they form an integral part, shall be described and justified.

For scaffolds, matrices and devices that fall under the definition of a medical device or active implantable medical device, the information required under section 17.3.4 for the evaluation of the combined advanced therapy medicinal product shall be provided.

17.3.3.2.2. Manufacturing process

The manufacturing process shall be validated to ensure batch and process consistency, functional integrity of the cells throughout manufacturing and transport up to the moment of application or administration, and proper differentiation state.

If cells are grown directly inside or on a matrix, scaffold or device, information shall be provided on the validation of the cell culture process with respect to cell-growth, function and integrity of the combination.

17.3.3.2.3. Characterization and control strategy

Relevant information shall be provided on the characterization of the cell population or cell mixture in terms of identity, purity (e.g. adventitious microbial agents and cellular contaminants),

viability, potency, karyology, tumourigenicity and suitability for the intended medicinal use. The genetic stability of the cells shall be demonstrated.

Qualitative and, where possible, quantitative information on product- and process-related impurities, as well as on any material capable of introducing degradation products during production, shall be provided. The extent of the determination of impurities shall be justified.

If certain release tests cannot be performed on the active substance or finished product, but only on key intermediates and/or as in-process testing, this shall be justified.

Where biologically active molecules (such as growth factors, cytokines) are present as components of the cell-based product, their impact and interaction with other components of the active substance shall be characterized.

(e) Where a three-dimensional structure is part of the intended function, the differentiation state, structural and functional organization of the cells and, where applicable, the extracellular matrix generated shall be part of the characterization for these cell-based products. Where needed, non-clinical investigations shall complement the physicochemical characterization.

17.3.3.2.4. Excipients

For excipient(s) used in cell or tissue-based medicinal products (e.g. the components of the transport medium), the requirements for novel excipients, as laid down in Part I of this Appendix, shall apply, unless data exists on the interactions between the cells or tissues and the excipients.

17.3.3.2.5. Developmental studies

The description of the development program shall address the choice of materials and processes. In particular, the integrity of the cell population as in the final formulation shall be discussed.

17.3.3.2.6. Reference materials

A reference standard, relevant and specific for the active substance and/or the finished product, shall be documented and characterized.

17.3.4. Specific requirements for advanced therapy medicinal products containing medical devices

17.3.4.1. Advanced therapy medicinal product containing medical devices

A description of the physical characteristics and performance of the product and a description of the product design methods shall be provided.

The interaction and compatibility between genes, cells and/or tissues and the structural components shall be described.

17.3.4.2. Combined advanced therapy medicinal products

‘Combined advanced therapy medicinal product’ means an advanced therapy medicinal product that fulfils the following conditions:

- it must incorporate, as an integral part of the product, one or more medical devices within the meaning of legal the definition of the Union or one or more active implantable medical devices within the meaning of the definition of the Union,
- its cellular or tissue part must contain viable cells or tissues,
- its cellular or tissue part containing non-viable cells or tissues must be liable to act upon the human body with action that can be considered as primary to that of the devices referred to.

For the cellular or tissue part of the combined advanced therapy medicinal product, the specific requirements for somatic cell therapy medicinal products and tissue engineered products set out in section 17.3.3 shall apply and, in the case of genetically modified cells, the specific requirements for gene therapy medicinal products set out in section 17.3.2 shall apply.

The medical device or the active implantable medical device may be an integral part of the active substance. Where the medical device or active implantable medical device is combined with the cells at the time of the manufacture or application or administration of the finished products, they shall be considered as an integral part of the finished product.

Information related to the medical device or the active implantable medical device (which is an integral part of the active substance or of the finished product) which is relevant for the evaluation of the combined advanced therapy medicinal product shall be provided. This information shall include:

- information on the choice and intended function of the medical device or implantable medical device and demonstration of compatibility of the device with other components of the product;
- evidence of conformity of the medical device part with the essential requirements laid down in the medical device legislation of the Union, or of conformity of the active implantable device part with the essential requirements laid down in legal acts which constitute the law of the Union in the medical device area;
- where applicable, evidence of compliance of the medical device or implantable medical device with the transmissible spongiform encephalopathies requirements;
- (where available, the results of any assessment of the medical device part or the active implantable medical device part by a competent authority (organization) in accordance with the legal acts which constitute the law of the Union in the medical device area (where necessary).

The notified body which has carried out the assessment referred to in point (d) of this section shall make available on request of the competent authority assessing the application, any information related to the results of the assessment in accordance with the legal acts which constitute the law of the Union in the medical device area. This may include information and documents contained in the conformity assessment application concerned, where necessary for the evaluation of the combined advanced therapy medicinal product as a whole.

17.4. Specific requirements regarding Module 4

17.4.1. Specific requirements for all advanced therapy medicinal products

The requirements of Part I, Module 4 of this Appendix on the pharmacological and toxicological testing of medicinal products may not always be appropriate due to unique and diverse structural and biological properties of advanced therapy medicinal products. The technical requirements in sections 17.4.1 to 17.4.3 below explain how the requirements in Part I of this Appendix apply to advanced therapy medicinal products. Where appropriate and taking into account the specificities of advanced therapy medicinal products, additional requirements have been set.

The rationale for the non-clinical development and the criteria used to choose the relevant species and models (in vitro and in vivo) shall be discussed and justified in the non-clinical overview. The chosen animal model(s) may include immuno-compromised, knockout, humanized or transgenic animals. The use of homologous models (e.g. mouse cells analyzed in mice) or disease mimicking models shall be considered, especially for immunogenicity and immunotoxicity studies.

In addition to the requirements of Part I of this Appendix, the safety, suitability and biocompatibility of all structural components (such as matrices, scaffolds and devices) and any additional substances (such as cellular products, biomolecules, biomaterials, and chemical substances), which are present in the finished product, shall be provided. Their physical, mechanical, chemical and biological properties shall be taken into account.

17.4.2. Specific requirements for gene therapy medicinal products

In order to determine the extent and type of non-clinical studies necessary to determine the appropriate level of non-clinical safety data, the design and type of the gene therapy medicinal product shall be taken into account.

17.4.2.1. Pharmacology

In vitro and in vivo studies of actions relating to the proposed therapeutic use (i.e. pharmacodynamic ‘proof of concept’ studies) shall be provided using models and relevant animal species designed to show that the nucleic acid sequence reaches its intended target (target organ or cells) and provides its intended function (level of expression and functional activity). The duration of the nucleic acid sequence function and the proposed dosing regimen in the clinical studies shall be provided.

Target selectivity: When the gene therapy medicinal product is intended to have a selective or target-restricted functionality, studies to confirm the specificity and duration of functionality and activity in target cells and tissues shall be provided.

17.4.2.2. Pharmacokinetics

Biodistribution studies shall include investigations on persistence, clearance and mobilisation. Biodistribution studies shall additionally address the risk of germline transmission.

Investigations of shedding and risk of transmission to third parties shall be provided with the environmental risk assessment, unless otherwise duly justified in the application on the basis of the type of product concerned.

17.4.2.3. Toxicology

Toxicity of the finished gene therapy medicinal product shall be assessed. In addition, depending on the type of product, individual testing of active substance and excipients shall be taken into consideration, the in vivo effect of expressed nucleic acid sequence-related products which are not intended for the physiological function shall be evaluated.

Single-dose toxicity studies may be combined with safety pharmacology and pharmacokinetic studies, e.g. to investigate persistence.

Repeated dose toxicity studies shall be provided when multiple dosing of human subjects is intended. The mode and scheme of administration shall closely reflect the planned clinical dosing. For those cases where single dosing may result in prolonged functionality of the nucleic acid sequence in humans, repeated toxicity studies shall be considered. The duration of the studies may be longer than in standard toxicity studies depending on the persistence of the gene therapy medicinal product and the anticipated potential risks. A justification for the duration shall be provided.

Genotoxicity shall be studied. However, standard genotoxicity studies shall only be conducted when they are necessary for testing a specific impurity or a component of the delivery system.

Carcinogenicity shall be studied. Standard lifetime rodent carcinogenicity studies shall not be required. However, depending on the type of product, the tumourigenic potential shall be evaluated in relevant in vivo/in vitro models.

Reproductive and developmental toxicity: Studies on the effects on fertility and general reproductive function shall be provided. Embryo-foetal and perinatal toxicity studies and germline transmission studies shall be provided, unless otherwise duly justified in the application on the basis of the type of product concerned.

Additional toxicity studies

Integration studies: integration studies shall be provided for any gene therapy medicinal product, unless the lack of these studies is scientifically justified, e.g. because nucleic acid sequences will not enter into the cell nucleus. For gene therapy medicinal products not expected to be capable of integration, integration studies shall be performed, if biodistribution data indicate a risk for germline transmission.

Immunogenicity and immunotoxicity: potential immunogenic and immunotoxic effects shall be studied.

17.4.3. Specific requirements for somatic cell therapy medicinal products and tissue engineered products

17.4.3.1. Pharmacology

The primary pharmacological studies shall be adequate to demonstrate the proof of concept. The interaction of the cell-based products with the surrounding tissue shall be studied.

The amount of product needed to achieve the desired effect/the effective dose, and, depending on the type of product, the frequency of dosing shall be determined.

Secondary pharmacological studies shall be taken into account to evaluate potential physiological effects that are not related to the desired therapeutic effect of the somatic cell therapy medicinal product, of the tissue engineered product or of additional substances, as biologically active molecules besides the protein(s) of interest might be secreted or the protein(s) of interest could have unwanted target sites.

17.4.3.2. Pharmacokinetics

Conventional pharmacokinetic studies to investigate absorption, distribution, metabolism and excretion shall not be required. However, parameters such as viability, longevity, distribution, growth, differentiation and migration shall be investigated, unless otherwise duly justified in the application on the basis of the type of product concerned.

For somatic cell therapy medicinal products and tissue engineered products, producing systemically active biomolecules, the distribution, duration and amount of expression of these molecules shall be studied.

17.4.3.3. Toxicology

The toxicity of the finished product shall be assessed. Individual testing of active substance(s), excipients, additional substances and any process-related impurities shall be taken into consideration.

The duration of observations may be longer than in standard toxicity studies and the anticipated lifespan of the medicinal product, together with its pharmacodynamic and pharmacokinetic profile, shall be taken into consideration. A justification of the duration shall be provided.

Conventional carcinogenicity and genotoxicity studies shall not be required, except with regard to the tumourigenic potential of the product.

Potential immunogenic and immunotoxic effects shall be studied.

In the case of cell-based products containing animal cells, the associated specific safety concerns such as transmission to humans of xenogeneic pathogens shall be addressed.

17.5. Specific requirements regarding Module 5

17.5.1. Specific requirements for all advanced therapy medicinal products

17.5.1.1. The specific requirements in this section of Part IV are additional requirements to those set in Module 5 in Part I of this Appendix.

17.5.1.2. Where the clinical application of advanced therapy medicinal products requires specific concomitant therapy and involve surgical procedures, the therapeutic procedure as a whole shall be investigated and described. Information on the standardization and optimization of those procedures during clinical development shall be provided.

Where medical devices used during the surgical procedures for application, implantation or administration of the advanced therapy medicinal product may have an impact on the efficacy or safety of the advanced therapy product, information on these devices shall be provided.

Specific expertise required to carry out the application, implantation, administration or follow-up activities shall be defined. Where necessary, the training plan of health care professionals on the use, application, implantation or administration procedures of these products shall be provided.

17.5.1.3. Given that, due to the nature of advanced therapy medicinal products, their manufacturing process may change during clinical development, additional studies to demonstrate comparability may be required.

17.5.1.4. During clinical development, risks arising from potential infectious agents or the use of material derived from animal sources and measures taken to reduce such risk shall be addressed.

17.5.1.5. Dose selection and schedule of use shall be defined by dose-finding studies.

17.5.1.6. The efficacy of the proposed indications shall be supported by relevant results from clinical studies using clinically meaningful endpoints for the intended use. In certain clinical conditions, evidence of long-term efficacy may be required. The strategy to evaluate long-term efficacy shall be provided.

17.5.1.7. A strategy for the long-term follow-up of safety and efficacy shall be included in the risk management plan.

17.5.1.8. For combined advanced therapy medicinal products, the safety and efficacy studies shall be designed for and performed on the combined product as a whole.

17.5.2. Specific requirements for gene therapy medicinal products

17.5.2.1. Human pharmacokinetic studies

Human pharmacokinetic studies shall include the following aspects:

shedding studies to address the excretion of the gene therapy medicinal products;

biodistribution studies;

pharmacokinetic studies of the medicinal product and the gene expression moieties (e.g. expressed proteins or genomic signatures).

17.5.2.2. Human pharmacodynamic studies

Human pharmacodynamic studies shall address the expression and function of the nucleic acid sequence following administration of the gene therapy medicinal product.

17.5.2.3. Safety studies

Safety studies shall address the following aspects:

emergence of replication competent vector;

emergence of new strains;

reassortment of existing genomic sequences;

neoplastic proliferation due to insertional mutagenicity.

17.5.3. Specific requirements for somatic cell therapy medicinal products

17.5.3.1. Somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s)

For somatic cell therapy medicinal products where the mode of action is based on the production of defined active biomolecule(s), the pharmacokinetic profile (in particular distribution, duration and amount of expression) of those molecules shall be addressed, if feasible.

17.5.3.2. Biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components

The biodistribution, persistence and long-term engraftment of the somatic cell therapy medicinal product components shall be addressed during the clinical development.

17.5.3.3. Safety studies

Safety studies shall address the following aspects:

distribution and engrafting following administration;

ectopic engraftment;

oncogenic transformation and cell/tissue lineage fidelity.

17.5.4. Specific requirements for tissue engineered products

17.5.4.1. Pharmacokinetic studies

Where conventional pharmacokinetic studies are not relevant for tissue engineered products, the biodistribution, persistence and degradation of the tissue engineered product components shall be addressed during the clinical development.

17.5.4.2. Pharmacodynamic studies

Pharmacodynamic studies shall be designed and tailored to the specificities of tissue engineered products. The evidence for the ‘proof of concept’ and the kinetics of the product to obtain the intended regeneration, repairing or replacement shall be provided. Suitable pharmacodynamic markers, related to the intended function(s) and structure shall be taken into account.

17.5.4.3. Safety studies

When investigating the safety of tissue-engineered products, section 17.5.3.3 of this Appendix shall apply.

APPENDIX 2
to the Rules of authorization and assessment of medicinal products for human use

TEMPLATES

of applications for a marketing authorization for a medicinal product, renewal of a marketing authorization, bringing into compliance with the requirements of the Eurasian Economic Union, and variation to a marketing authorization for a medicinal product

(template)

I. APPLICATION FOR A MARKETING AUTHORIZATION FOR A MEDICINAL PRODUCT (BRINGING INTO COMPLIANCE WITH THE REQUIREMENTS OF THE EURASIAN ECONOMIC UNION)

The date the application received «___» _____ 20__ г. № _____

Brand names of a medicinal product	
Active substances	
Strengths and dosage form	
Presentation	
Marketing authorization holder	
Applicant	
Applicant’s representative	

It is hereby confirmed that information in documents and particulars of the marketing authorization application dossier is reliable.

It is hereby confirmed that in case of failure to submit documents and particulars of the marketing authorization application dossier in response of observations of the competent authority (assessment organization) of the reference Member State within a maximum of 90 days, evaluation of the application shall be refused.

It is hereby confirmed that all existing marketing authorization application dossier data have been obtained in accordance with applicable legislation and that such data does not violate intellectual rights of a third party (subsections 4.3 and 4.2 of Appendix to this application).

It is hereby confirmed that fees will be paid/have been paid according to the rules.

A letter for authorization for taking legal actions on behalf of the marketing authorization holder is provided (Section 4.1 of the Appendix to this application).

On behalf of the applicant

_____
(signature)

_____
(name)

_____
(title)

SEAL

1. Common sections of the application

1.1. This application is submitted in accordance with the following.

1.1.1. The application is submitted under the mutual recognition procedure:

Reference Member State	
Brand name in the reference Member State	
Date of granting a marketing authorization	
Number of a certificate of a marketing authorization	
Copy of a certificate of a marketing authorization	
Marketing authorization application number	
Member States concerned where the medicinal product has already been authorized for marketing (where appropriate)	
Brand names in Member States concerned (where differ from that approved in the reference Member State), where the medicinal product has already been authorized for marketing	
Date of granting a marketing authorization in Member States concerned, if the medicinal product has been authorized for marketing	
Number of a certificate of a marketing authorization in Member States concerned	
Other Eurasian Economic Union Member States for application submission (where appropriate)	
Brand names in Member States concerned (where differ from that approved in the reference Member State and/or Member States concerned (as appropriate))	

1.1.2. The application is submitted under the decentralized procedure:

Application number	
Reference Member State	
Brand name in the reference Member State	
Member States concerned for application submission	
Brand names in Member States concerned (where differ from that approved in the reference Member State and/or Member States concerned (as appropriate))	

1.1.3. The application is submitted in view of bringing a marketing authorization application dossier into compliance with the requirements of the Eurasian Economic Union under mutual recognition procedure:

Reference Member State	
Brand name in the reference Member State	
Date of granting a marketing authorization	
Number of a certificate of a marketing authorization	
Copy of a certificate of a marketing authorization	
Number of an application for bringing into compliance with the requirements of the Eurasian Economic Union	
Eurasian Economic Union Member States where the medicinal product has already been authorized, where available	
Brand names in Member States concerned where the medicinal product has already been authorized for marketing (where differ from that approved in the reference Member State)	
Date of granting a marketing authorization in Member States concerned, if the medicinal product has been authorized for marketing	
Number of a certificate of a marketing authorization in Member States concerned	

Note: This section shall be completed for each application including those referenced in this section.

When an application for the appropriate medicinal product type is submitted, other sections of the application on other medicinal product types shall not be completed.

☐ ORIGINAL MEDICINAL PRODUCT

☐ biological medicinal product ☐ other medicinal product

☐ new active substance (hereinafter referred to as API)

Note: No information on API in the Common Register of the Authorized Medicinal Products of the Eurasian Economic Union or in the appropriate national registers Eurasian Economic Union Member States.

☐ known API

Note: there is information on API in the Common Register of the Authorized Medicinal Products of the Eurasian Economic Union or in the appropriate national registers Eurasian Economic Union Member States.

☐ GENERIC MEDICINAL PRODUCT

☐ one API ☐ more than one API

Original medicinal product:

Name of the medicinal product, strength, dosage form	

Marketing authorization holder (company holding marketing authorization), date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the original medicinal product has been authorized	

Reference medicinal product used in equivalence studies (where conducted):

Name of the medicinal product, strength, dosage form	
Marketing authorization holder (company holding marketing authorization), date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the reference medicinal product has been authorized	
Justification for using reference product where it differs from original product shall be supplied	
Any Expert Committee on medicinal products recommendations for a reference medicinal product selection	

Note:

1. The section shall be completed for each medicinal product used in equivalence studies.

2. When completing an application, in the *original medicinal product* section, information on the original medicinal product chosen as a reference for generic medicinal product shall be provided. In the *reference medicinal product* section, information on the reference medicinal product chosen to demonstrate equivalence shall be provided. When both are the same, information on reference medicinal product and original medicinal product shall be repeated.

☐ SIMILAR BIOLIGICAL MEDICINAL PRODUCT (BIOSIMILAR)

Original biological medicinal product:

Name of the medicinal product, strength, dosage form	
Marketing authorization holder (company holding marketing authorization), date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the original medicinal product has been authorized	

Reference biological medicinal product:

Name of the medicinal product, strength, dosage form	
Marketing authorization holder, date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the	

reference medicinal product has been authorized	
Any Expert Committee on medicinal products recommendations for a reference medicinal product selection	
Differences with the reference biological medicinal product (as appropriate):	☐ different starting materials ☐ different manufacturing process ☐ different therapeutic indications ☐ different pharmaceutical form ☐ different strengths (qualitative difference in AS) ☐ different route of administration ☐ other differences: _____ _____

Note: When completing an application, in the *original biological medicinal product* section, information on the original biological medicinal product chosen as a reference for biosimilar medicinal product shall be provided. In the *reference medicinal product* section, information on the reference medicinal product(s) chosen to demonstrate biosimilarity shall be provided. When both are the same, information on reference medicinal product and original medicinal product shall be repeated.

☐ HYBRID MEDICINAL PRODUCT

Original medicinal product:

Name of the medicinal product, strength, dosage form	
Marketing authorization holder, date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the original medicinal product has been authorized	
Differences with the original medicinal product:	☐ different active substance ☐ different pharmaceutical form ☐ different strengths (qualitative difference in AS) ☐ different route of administration ☐ different pharmacokinetics (including different bioavailability); ☐ differences in therapeutic indications ☐ other differences: _____ _____

Note: When completing an application, in this section, information on the original medicinal product chosen as a reference for hybrid medicinal product shall be provided. This section shall be completed regardless marketing status of the original medicinal product.

☐ COMBINATION MEDICINAL PRODUCT

☐ known combination ☐ new combination

Original medicinal product (in case of a known combination):

Name of the medicinal product, strength, dosage form	
Marketing authorization holder, date of	

granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the original medicinal product has been authorized	

☐ WELL-ESTABLISHED MEDICINAL PRODUCT

☐ RADIOPHARMACEUTICAL OR PRECURSOR

☐ radiopharmaceutical kit

☐ radionuclide precursor

radionuclide source (primary or secondary) (where available)	
generator	

☐ HOMEOPATHIC MEDICINAL PRODUCT

☐ new homeopathic product not included in pharmacopoeias or monographs

☐ homeopathic product included in pharmacopoeias or monographs

☐ HERBAL MEDICINAL PRODUCT

☐ VARIATIONS ENTAILING GRANTING NEW MARKETING AUTHORIZATION (EXTENTIONS)

Check as appropriate:

☐ changes to the active substances not considered new API:

☐ replacement of a chemical active substance by a different salt/ester complex/derivative, with the same therapeutic moiety, where the efficacy/safety characteristics are not significantly different;

☐ replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer), where the efficacy/safety characteristics are not significantly different;

☐ replacement of a biological active substance with one of a slightly different molecular structure where the efficacy/safety characteristics are not significantly different, with the exception of changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

☐ modification of the vector used to produce the antigen or the source material, including a new master cell bank from a different source, where the efficacy/safety characteristics are not significantly different;

☐ a new ligand or coupling mechanism for a radiopharmaceutical, where the efficacy/safety characteristics are not significantly different;

☐ change to the extraction solvent or the ratio of herbal drug to herbal drug preparation where the efficacy/safety characteristics are not significantly different;

☐ changes to strength, pharmaceutical form and route of administration:

☐ change of bioavailability;

☐ change of pharmacokinetics;

☐ change or addition of a new strength/potency;

☐ change or addition of a new pharmaceutical form;

☐ change or addition of a new route of administration

Medicinal product authorized for marketing in the reference Member State _____ and which is subject to the appropriate variations:
(name of the Member State)

Brand name of the medicinal product, strength, dosage form	
Marketing authorization holder, date of granting a marketing authorization	
Number of a certificate of a marketing authorization	

☐ ORPHAN MEDICINAL PRODUCT

Has orphan designation been granted in the Eurasian Economic Union or elsewhere

☐ no ☐ pending ☐ yes

Date	
Number of a certificate of a marketing authorization for an orphan medicinal product	
Eurasian Economic Union Member States and/or other countries which have designated the medicinal product as orphan	

Orphan designation has been refused:

Date	
Decision number	
Application for designation has been withdrawn	
Date	

A copy of a document confirming orphan designation for a medicinal product (where available) (subsection 4.2 of Appendix to this application).

2. Specific sections of the application

2.1. Name and ATC code

2.1.1. Name of the medicinal product

2.1.2. API name or composition

Note: only one name shall be given in the following order of priority: international nonproprietary name (hereinafter referred to as INN)*, name provided in the Pharmacopoeia of the Eurasian Economic Union or pharmacopoeias of Member States (or main pharmacopeias in accordance with the Eurasian Economic Union Member States Pharmacopeia Harmonization Conception), usual common name, scientific (chemical) name.

* The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant

2.1.3. Pharmacotherapeutic group

(Please use current ATC code)

ATC code	
Group	

If no ATC code has been assigned, please indicate if an application for ATC code has been made

2.2. Strength, dosage form, route of administration, container and pack sizes

2.2.1. Strength and dosage form

(use current list of standard terms of the Eurasian Economic Union Pharmaceutical Form Nomenclature)

Dosage form	
Strengths	
2.2.2. Route of administration (use current list of standard terms of the Pharmaceutical Form Nomenclature)	
2.2.3. Container, closure and administration device(s), including description of material from which it is constructed (use current list of standard terms of the Pharmaceutical Form Nomenclature)	

For each packaging type please provide:
2.2.3.1. Package size (number of dosage units).
2.2.3.2. Proposed shelf life.
2.2.3.3. Proposed shelf life (after first opening container).
2.2.3.4. Proposed shelf life (after reconstitution or dilution).
2.2.3.5. Proposed storage conditions.
2.2.3.6. Proposed storage conditions after first opening.

2.2.4. Information on delivery devices

2.3. Legal status

2.3.1. Proposed dispensing/classification:

☐ subject to medical prescription
☐ not subject to medical prescription
☐ in hospital settings

2.4. Marketing authorization holder

2.4.1. Marketing authorization holder:

Company name	
Address	
Country	
Telephone and telefax, where available	
E-Mail	

2.4.2. Marketing authorization holder representative (Person/company authorised for communication on behalf of the marketing authorization holder representative during the procedure, i.e. applicant):

Name	

Telephone and telefax, where available	
E-Mail	

When completing this section, a letter for authorization for taking legal actions on behalf of the marketing authorization holder shall be provided (Section 4.1 of the Appendix to this application).

2.4.3. Person/Company authorized for communication between the marketing authorization holder and the competent authorities after authorization if different from 2.4.2

Name	
Company address	
Country	
Telephone and telefax, where available	
E-Mail	

When completing this section, a letter for authorization shall be provided (section 4.1 of the Appendix to this application).

2.4.4. The marketing authorization holder's qualified person responsible for pharmacovigilance in the Eurasian Economic Union Member States:

Name of the qualified person responsible for pharmacovigilance	
Company name (of the marketing authorization holder)	
Company address (of the marketing authorization holder)	
Country	
24 H Telephone and Telefax	
E-Mail	

Address where the marketing authorization holder's qualified person responsible for pharmacovigilance resides and lives.

Pharmacovigilance system master file: Number: Address:

2.4.5. The marketing authorization holder's qualified person responsible for pharmacovigilance in the Eurasian Economic Union Member States where differs from that referred to in section 2.4.4:

Name of the qualified person responsible for pharmacovigilance	
Company name (of the marketing authorization holder)	
Company address	
Country	
24 H Telephone and Telefax	
E-Mail	

Address where the marketing authorization holder's contact person responsible for

pharmacovigilance resides and lives.

2.5. Manufacturer

2.5.1. Authorized manufacturer responsible for batch release (as shown in the summary of product characteristics, package leaflet, and where applicable in the labelling)

Company name	
Address	
Country	
Telephone and telefax, where available	
E-Mail	

2.5.2. Manufacturer's quality control laboratory responsible for batch release for blood products and vaccines

Laboratory name	
Address	
Country	
Telephone and telefax, where available	
E-Mail	

2.5.3. Contact person in the Eurasian Economic Union (for each Member State, where appropriate) for product defects and recalls

Company name	
Address	
Country	
24 H Telephone and Telefax	
E-Mail	

2.5.4. Manufacturer of the medicinal product and sites of manufacture

All manufacturing sites involved in manufacturing process of the medicinal product including solvents specifying the manufacturing step:

Manufacturing step name*, company name*	
Address*	
Country*	
Telephone and telefax, where available*	
E-Mail*	

* For each site provide the relevant information (attach flow-chart indicating the sequence and activities of the different sites involved in the manufacturing process, including batch release)

Has the site been inspected for compliance with the requirements of the Good Manufacturing Practice of the Eurasian Economic Union by the competent authority of the Eurasian Economic Union Member State:

☐ no ☐ yes

If yes, please provide:

The date of the latest inspection	
Competent authority name which carried out the inspection	
Inspection type	
Type of medicinal products and APIs inspected	
Conclusion	compliant: ☐ no ☐ yes

Has the site been inspected for compliance with the requirements of the Good Manufacturing Practice by the other country's competent authority

☐ no ☐ yes

If yes, please provide:

Date of the latest inspection	
Competent authority name which carried out the inspection	
Inspection type	
Type of medicinal products and APIs inspected	
Conclusion	compliant: ☐ no ☐ yes

2.5.5. Manufacturer of the API and sites of manufacture

All manufacturing sites involved in the manufacturing process of each API specifying the manufacturing step. For biotech products include all sites of storage of master and working cell bank and preparation of working cell banks:

Manufacturing step name, active substance	
Company name, name of the entrepreneur	
Address	
Country	
Telephone and telefax, where available	
E-Mail	

For each active substance, attach a Qualified Person declaration in accordance with section 4.5 of the Appendix to this application (attach flow-chart indicating the sequence and activities of the different sites involved in the manufacturing process, including testing sites).

Has the API site been inspected for compliance with the requirements of the Rules of the Good Manufacturing Practice of the Eurasian Economic Union by the competent authority of the Eurasian Economic Union Member State:

☐ no ☐ yes

Has a Ph.Eur. Certificate of suitability been issued for the API:

☐ no ☐ yes

If yes:

Active substance name	
Company name or name of the entrepreneur (manufacturer)	
CEP number	
Date of last update	

Has the API site been inspected for compliance with the requirements of the Good Manufacturing Practice by the other country's competent authority:

☐ no ☐ yes

If yes, please provide:

Date of the latest inspection	
Competent authority name which carried out the inspection	
Inspection type	
Compliance document number	
Conclusion	compliant: ☐ no ☐ yes

Is an Active Substance Master File to be used for the active substance:

☐ no ☐ yes

If yes:

Active substance name	
Name of the Active Substance Master File holder	
Name of the API manufacturer if different from the Active Substance Master File holder	
Date of last update	

Is a certificate for a Vaccine Antigen Master File (hereinafter referred to as VAMF) been issued or submitted for issuance, being used for this MAA:

☐ no ☐ yes

If yes:

Vaccine antigen name	
Vaccine antigen manufacturer's/VAMF certificate holder's name	
Reference number of Application/Certificate	
Date of submission (if pending)	
Date of approval or last update	

2.5.6. Contract companies used for clinical trial(s) on bioavailability or bioequivalence or used for the validation of blood product manufacturing processes

For each contract company, state where analytical tests are performed and where clinical data are

collected and give:

Title of the study	
Protocol code	
EudraCT-Number, if appropriate	
ClinicalTrials.gov-number, if appropriate	
Name of the contract research organization	
Address	
Telephone and telefax, where available	
E-Mail	

2.6. Qualitative and quantitative composition of the medicinal product

2.6.1. Qualitative and Quantitative composition in terms of the active substance and the excipients of the medicinal product:

A note should be given as to which quantity the composition refers (e.g. per unit, per unit-volume, per unit-mass, etc.).
List the API separately from the excipients:

№	API name	Quantity (mass, volume, or potency units)	Unit	Reference/Monograph standard
№	Excipient name	Quantity (mass, volume, or potency units)	Unit	Reference/Monograph standard

Note: only one name shall be given in the following order of priority: INN*, name provided in the Pharmacopoeia of the Eurasian Economic Union or pharmacopoeias of Member States (or main pharmacopeias in accordance with the Eurasian Economic Union Member States Pharmacopeia Harmonization Conception), usual common name, scientific (chemical) name.
* The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant.

Details of any overages should not be included in the formulation columns but stated below:

Active substances	
Excipients	

2.6.2. List of materials of animal and/or human origin contained or used in the manufacturing process of the medicinal product

☐ NONE

Name	Function			Animal origin susceptible to TSE[3]	Other animal origin	Human origin	Ph.Eur. certificate of suitability for TSE[3] (where available)
	API	EX[1]	R[2]				
1							

2							
3							
…							

Specify whether a TSE Certificate of Suitability to the monograph of the European Pharmacopoeia or a document issued by the competent authority for animal health of the county of substance origin (based on clinical and laboratory control) on TSE[3] cases

[1] EX=excipient (incl. starting materials used in the manufacture of the active substance/excipient).
[2] R=reagent/culture medium (incl. those used in the preparation of master and working cell banks).
[3]TSE=transmissible spongiform encephalopathy.

2.6.3. Is a certificate for a Plasma Master File (hereinafter referred to as PMF) been issued or submitted for issuance, being used for this MAA:

☐ no ☐ yes

If yes:

Substance referring to PMF			
Function	AS	EX[1]	R[2]
Name of the PMF Certificate Holder/ PMF Applicant			
Reference number of Application/Certificate			
Date of submission (if pending)			
Date of approval or last update (if approved)			

[1] EX=excipient (incl. starting materials used in the manufacture of the active substance/excipient).
[2] R=reagent/culture medium (incl. those used in the preparation of master and working cell banks).

2.6.4. Does the medicinal product contain or consist of Genetically Modified Organisms (GMOs):

☐ no ☐ yes

If yes, does the product comply established requirements:

☐ no ☐ yes

Provide necessary reference.

3. Other information

3.1. Are the intellectual rights for a medicinal product protected by patents effective within the Eurasian Economic Union Member State:

☐ no ☐ yes

If yes, please provide the following information:

Patent number	Effective within the Member State	Date of issuance	Effective by	Patent holder

For granting a marketing authorization for medicinal products (bringing a marketing authorization dossier of a medicinal product into compliance with the legal acts which constitute the law of the Eurasian Economic Union) having a patent issued in accordance with the Eurasian Economic Union Member State legislation, the applicant shall apply a certified copy of that patent or license agreement authorizing manufacturing or marketing an authorized medicinal product. Applicants shall provide a letter declaring that the intellectual rights of a third parties protected by the patent or transferred in accordance with the license are not violated due to the marketing authorization.

3.2. Has a trademark been approved in the Eurasian Economic Union Member States:

☐ no ☐ yes

If yes, please provide the following information:

Certificate number	Effective within the Member State	Date of issuance	Effective by	Certificate holder

A certified copy of the trademark certificate effective within the Eurasian Economic Union Member State shall be provided.

Where the applicant differs from the certificate holder, a copy of the license agreement certified by the applicant or a confirmation of a franchise for the trademark.

3.3. Has the manufacturer's country granted an authorization for the same medicinal product:

☐ no ☐ yes

Is there another countries where an authorization is granted for the same product:

☐ no ☐ yes

3.4. Was there scientific advice(s) given by Eurasian Economic Union Member States for this medicinal product:

☐ no ☐ yes

If yes:

Member State	
Date	
Reference of the scientific advice	

Was there scientific advice(s) given by the Expert Committee for medicinal products for this medicinal product:

☐ no ☐ yes

If yes:

Date	
Reference of the scientific advice	

3.5. Information on whether an authorization was refused/ suspended/ revoked manufacturer's country or other countries for the same product.

☐ no ☐ yes

If yes:

Type of restriction	Reason	Country	Period	Date
…				

4. Appendices to the application

4.1. A letter for authorization for taking legal actions on behalf of the marketing authorization holder, if appropriate.

4.2. A copy the document confirming orphan designation for a medicinal product.

4.3. Copies of patents for the applied medicinal product effective within Eurasian Economic Union Member State.

4.4. Written confirmation that the intellectual rights of a third parties protected by the patent or transferred in accordance with the license are not violated due to the marketing authorization.

4.5. A certified copy of the trademark certificate effective within the Eurasian Economic Union Member State.

4.6. A declaration(s) from the Qualified Person of the manufacturing authorization holder that each manufacturing site where the medicinal product and active substance is manufactured including testing sites is in compliance the Rules of the Good Manufacturing Practice of the Eurasian Economic Union subject to approval by the Commission and guidelines of good manufacturing practice for starting materials.

II. APPLICATION
FOR RENEWAL OF A MARKETING AUTHORIZATION

The date the application received № _____
«___» _____ 20__ г.

Brand names of a medicinal product	
Active substances	
Strengths	
Dosage form	
Presentation	
Marketing authorization holder	
Applicant	
Applicant's representative	
Certificate of Marketing authorization data	
Number of a certificate of a marketing authorization	
Date of granting a marketing authorization	
Normative document number	

It is hereby confirmed that information in documents and particulars of the marketing authorization application dossier is reliable.
It is hereby confirmed that in case of failure to submit documents and particulars of the marketing authorization application dossier in response of observations of the competent authority (assessment organization) of the reference Member State within a maximum of 30 days, evaluation of the application shall be refused.
It is hereby confirmed that all existing marketing authorization application dossier data have been obtained in accordance with applicable legislation and that such data does not violate intellectual rights of a third party (subsections 5.3 and 5.4 of the Appendix to this application).
It is hereby confirmed that fees will be paid/have been paid according to the rules.

A letter for authorization for taking legal actions on behalf of the marketing authorization holder is provided (subsection 5.1 of the Appendix to this application).

On behalf of the applicant

_____
(signature)

_____
(name)

_____
(title)

SEAL

1. Common sections of the application

1.1. This application is submitted in accordance with the following.

1.1.1. The application is submitted under the mutual recognition procedure:

Reference Member State	
Brand name in the reference Member State	
Date of granting a marketing authorization	
Number of a certificate of a marketing authorization	
Copy of a certificate of a marketing authorization	
Application number	
Other Eurasian Economic Union Member States for application (where appropriate)	
Brand names in Member States concerned (where differ from that approved in the reference Member State)	

1.1.2. The application is submitted under the decentralized procedure:

Application number	
Reference Member State	
Brand name in the reference Member State	
Member States concerned for application submission	
Brand names in Member States concerned (where differ from that approved in the reference Member State)	

Note: This section shall be completed for each application including those referenced in this section.

2. Approved or pending variations since the marketing authorization has been granted

№	Date of submission	Date of approval	Variation type (type of procedure), brief description of the variation
…			

When an application for the appropriate medicinal product type is submitted, other sections of the application on other medicinal product types shall not be completed.

☐ ORIGINAL MEDICINAL PRODUCT

☐ biological medicinal product	☐ other medicinal product
☐ new active substance (hereinafter referred to as API) Note: No information on API in the Common Register of the Authorized Medicinal Products of the Eurasian Economic Union or in the appropriate national registers Eurasian Economic Union Member States.	
☐ known API Note: There is information on API in the Common Register of the Authorized Medicinal Products of the Eurasian Economic Union or in the appropriate national registers Eurasian Economic Union Member States.	

☐ GENERIC MEDICINAL PRODUCT

☐ one AS ☐ more than one AS

Original medicinal product:	
Name of the medicinal product, strength, dosage form	
Marketing authorization holder (company holding marketing authorization), date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the original medicinal product has been authorized	
Reference medicinal product used in equivalence studies (where conducted):	
Name of the medicinal product, strength, dosage form	
Marketing authorization holder (company holding marketing authorization), date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the reference medicinal product has been authorized	
Justification for using reference product where it differs from original product shall be supplied	
Any Expert Committee on medicinal products recommendations for a reference medicinal product selection	

Note: The section shall be completed for each medicinal product used in equivalence studies.

☐ SIMILAR BIOLIGICAL MEDICINAL PRODUCT (BIOSIMILAR)

Original biological medicinal product:

Name of the medicinal product, strength, dosage form	
Marketing authorization holder (company holding marketing authorization), date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the original medicinal product has been authorized	

Reference biological medicinal product:

Name of the medicinal product, strength, dosage form	
Marketing authorization holder, date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the reference medicinal product has been authorized	
Any Expert Committee on medicinal products recommendations for a reference medicinal product selection	
Differences with the reference biological medicinal product (as appropriate):	☐ different starting materials ☐ different manufacturing process ☐ different therapeutic indications ☐ different pharmaceutical form ☐ different strengths (qualitative difference in API) ☐ different route of administration ☐ other differences: _____ _____

☐ HYBRID MEDICINAL PRODUCT

Original medicinal product:	
Name of the medicinal product, strength, dosage form	
Marketing authorization holder, date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the original medicinal product has been authorized	
Differences with the original medicinal product:	☐ different active substance ☐ different pharmaceutical form ☐ different strengths (qualitative difference in API) ☐ different route of administration ☐ different pharmacokinetics (including different bioavailability); ☐ differences in therapeutic indications ☐ other differences: _____

☐ COMBINATION MEDICINAL PRODUCT

☐ known combination ☐ new combination

Original medicinal product (in case of a known combination):

Name of the medicinal product, strength, dosage form	
Marketing authorization holder, date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the original medicinal product has been authorized	

☐ WELL-ESTABLISHED MEDICINAL PRODUCT

☐ RADIOPHARMACEUTICAL OR PRECURSOR

☐ radiopharmaceutical kit

 radionuclide precursor

radionuclide source (primary or secondary) (where available)	
generator	

☐ HOMEOPATHIC MEDICINAL PRODUCT

☐ new homeopathic product not included in pharmacopoeias or monographs

☐ homeopathic product included in pharmacopoeias or monographs

☐ HERBAL MEDICINAL PRODUCT

☐ ORPHAN MEDICINAL PRODUCT

Has orphan designation been granted in the Eurasian Economic Union or elsewhere

☐ no ☐ pending ☐ yes

Date	
Number of a certificate of a marketing authorization for an orphan medicinal product	
Eurasian Economic Union Member States and/or other countries which have designated the medicinal product as orphan	

Orphan designation has been refused:

Date	
Decision number	
Application for designation has been withdrawn	
Date	
A copy of a document confirming orphan designation for a medicinal product (where available) (subsection 5.2 of Appendix to this application).	

3. Specific sections of the application

3.1. Name and ATC code	
3.1.1. Name of the medicinal product	
3.1.2. API name or composition	

Note: only one name shall be given in the following order of priority: international nonproprietary name (hereinafter referred to as INN)*, name provided in the Pharmacopoeia of the Eurasian Economic Union or pharmacopoeias of Member States (or main pharmacopeias in accordance with the Eurasian Economic Union Member States Pharmacopeia Harmonization Conception), usual common name, scientific (chemical) name.

* The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant

3.1.3. Pharmacotherapeutic group

(Please use current ATC code)

ATC code	
group	

If no ATC code has been assigned, please indicate if an application for ATC code has been made

3.2. Strength, dosage form, route of administration, container and pack sizes

3.2.1. Strength and Dosage form

(use current list of standard terms of the Eurasian Economic Union Pharmaceutical Form Nomenclature)

Dosage form	
Strengths	
3.2.2. Route of administration (use current list of standard terms of the Pharmaceutical Form Nomenclature)	
3.2.3. Container, closure and administration device(s), including description of material from which it is constructed (use current list of standard terms of the Pharmaceutical Form Nomenclature)	

For each packaging type please provide:
3.2.3.1. Package size (number of dosage units).
3.2.3.2. Proposed shelf life.
3.2.3.3. Proposed shelf life (after first opening container).
3.2.3.4. Proposed shelf life (after reconstitution or dilution).
3.2.3.5. Proposed storage conditions.
3.2.3.6. Proposed storage conditions after first opening of the container or intermediate packaging.

3.2.4. Information on delivery devices

3.3. Legal status

3.3.1. Proposed dispensing/classification:

☐ subject to medical prescription
☐ not subject to medical prescription
☐ in hospital settings

3.4. Marketing authorization holder

3.4.1. Marketing authorization holder:

Company name	
Address	
Country	
Telephone and telefax, where available	
E-Mail	

3.4.2. Marketing authorization holder representative (Person/company authorized for communication on behalf of the marketing authorization holder representative during the procedure, i.e. applicant):

Name	
Telephone and telefax, where available	
E-Mail	

When completing this section, a letter for authorization for taking legal actions on behalf of the marketing authorization holder shall be provided (Section 5.1 of the Appendix to this application).

3.4.3. Person/Company authorized for communication between the marketing authorization holder and the competent authorities after authorization if different from 3.4.2:

Name	
Company address	
Country	
Telephone and telefax, where available	
E-Mail	

When completing this section, a letter for authorization shall be provided (section 5.1 of the Appendix to this application).

3.4.4. The marketing authorization holder's qualified person responsible for pharmacovigilance in the Eurasian Economic Union Member States:

Name of the qualified person responsible for pharmacovigilance	
Company name (of the marketing authorization holder)	
Company address (of the marketing authorization holder)	
Country	
24 H Telephone and Telefax	
E-Mail	

Address where the marketing authorization holder's qualified person responsible for pharmacovigilance resides and lives.

Pharmacovigilance system master file: Number:

Address:

3.4.5. The marketing authorization holder's qualified person responsible for pharmacovigilance in the Eurasian Economic Union Member States where differs from that referred to in section 3.4.4:

Name of the qualified person responsible for pharmacovigilance	
Company name (of the marketing authorization holder)	
Company address	
Country	
24 H Telephone and Telefax	
E-Mail	

Address where the marketing authorization holder's qualified person responsible for pharmacovigilance resides and lives.

3.5. Manufacturer

3.5.1. Authorized manufacturer responsible for batch release (as shown in the summary of product characteristics, package leaflet, and where applicable in the labelling)

Company name	
Address	
Country	
Telephone and telefax, where available	
E-Mail	

3.5.2. Manufacturer's quality control laboratory responsible for batch release for blood products and vaccines

Laboratory name	
Address	
Country	
Telephone and telefax, where available	
E-Mail	

3.5.3. Contact person in the Eurasian Economic Union (for each Member State, where appropriate) for product defects and recalls

Company name	
Address	
Country	
24 H Telephone and Telefax	
E-Mail	

3.5.4. Manufacturer of the medicinal product and sites of manufacture:

All manufacturing sites involved in manufacturing process of the medicinal product including solvents specifying the manufacturing step

Manufacturing step name*, company name*	
Address*	
Country*	
Telephone and telefax, where available*	
E-Mail*	

* For each site provide the relevant information (attach flow-chart indicating the sequence and activities of the different sites involved in the manufacturing process, including testing sites).

Has the site been inspected for compliance with the requirements of the Good Manufacturing Practice of the Eurasian Economic Union by the competent authority of the Eurasian Economic Union Member State:

☐ no ☐ yes

If yes, please provide:

Date of the latest inspection	
Competent authority name which carried out the inspection	
Inspection type	
Type of medicinal products and APIs inspected	
Conclusion	compliant: ☐ no ☐ yes

Has the site been inspected for compliance with the requirements of the Good Manufacturing Practice by the other country's competent authority (organization):

☐ no ☐ yes

If yes, please provide:

The date of the latest inspection	
Competent authority name which carried out the inspection	
Inspection type	
Type of medicinal products and ASs inspected	
Conclusion	compliant: ☐ no ☐ yes

3.5.5. Manufacturer of the API and sites of manufacture

All manufacturing sites involved in the manufacturing process of each API specifying the manufacturing step. For biotech products include all sites of storage of master and working cell bank and preparation of working cell banks:

Manufacturing step name, active substance	
Company name, name of the entrepreneur	
Address	
Country	
Telephone and telefax, where available	
E-Mail	

For each active substance, attach a Qualified Person declaration in accordance with section 5.5 of the Appendix to this application (attach flow-chart indicating the sequence and activities of the different sites involved in the manufacturing process, including testing sites).

Has the API site been inspected for compliance with the requirements of the Rules of the Good Manufacturing Practice of the Eurasian Economic Union by the competent authority of the Eurasian Economic Union Member State:

☐ no ☐ yes

Has a Ph.Eur. Certificate of suitability been issued for the AS:

☐ no ☐ yes

If yes:

Active substance name	
Company name or name of the entrepreneur (manufacturer)	
CEP number	
Date of last update	

Has the API site been inspected for compliance with the requirements of the Good Manufacturing Practice by the other country's competent authority (organization):

☐ no ☐ yes

If yes, please provide:

Date of the latest inspection	
Competent authority name which carried out the inspection	
Inspection type	
Compliance document number	
Conclusion	compliant: ☐ no ☐ yes

Is an Active Substance Master File to be used for the active substance:

☐ no ☐ yes

If yes:

Active substance name	
Name of the Active Substance Master File holder	
Name of the API manufacturer if different from the Active Substance Master File holder	
Date of last update	

Is a certificate for a Vaccine Antigen Master File (hereinafter referred to as VAMF) been issued or submitted for issuance, being used for this MAA:

☐ no ☐ yes

If yes:

Vaccine antigen name	

Vaccine antigen manufacturer's/VAMF certificate holder's name	
Reference number of Application/Certificate	
Date of submission (if pending)	
Date of approval or last update	

3.5.6. Contract companies used for clinical trial(s) on bioavailability or bioequivalence or used for the validation of blood product manufacturing processes

For each contract company, state where analytical tests are performed and where clinical data are collected and give:

Title of the study	
Protocol code	
EudraCT-Number, if appropriate	
ClinicalTrials.gov-number, if appropriate	
Name of the contract research organization	
Address	
Telephone and telefax, where available	
E-Mail	

3.6. Qualitative and quantitative composition of the medicinal product

3.6.1. Qualitative and Quantitative composition in terms of the active substance and the excipients of the medicinal productA note should be given as to which quantity the composition refers (e.g. per unit, per unit-volume, per unit-mass, etc.).

List the API separately from the excipients:

№	API name*	Quantity (mass, volume, or potency units)	Unit	Reference/Monograph standard
№	Excipient name	Quantity (mass, volume, or potency units)	Unit	Reference/Monograph standard

Note: only one name shall be given in the following order of priority: INN**, name provided in the Pharmacopoeia of the Eurasian Economic Union or pharmacopoeias of Member States (or main pharmacopeias in accordance with the Eurasian Economic Union Member States Pharmacopeia Harmonization Conception), usual common name, scientific (chemical) name.

_____

** The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant.

Details of any overages should not be included in the formulation columns but stated below:

Active substances	
Excipient(s)	

3.6.2. List of materials of animal and/or human origin contained or used in the manufacturing process of the medicinal product

☐ NONE

Name	Function			Animal origin susceptible to TSE[3]	Other animal origin	Human origin	Ph.Eur. certificate of suitability for TSE[3] (where available)
	API	EX[1]	P[2]				
1							
2							
3							
....							

Specify whether a TSE Certificate of Suitability to the monograph of the European Pharmacopoeia or a document issued by the competent authority for animal health of the county of substance origin (based on clinical and laboratory control) on TSE[3] cases.

[1] EX=excipient (incl. starting materials used in the manufacture of the active substance/excipient).
[2] R=reagent/culture medium (incl. those used in the preparation of master and working cell banks).
[3] TSE=transmissible spongiform encephalopathy.

3.6.3. Is a certificate for a Plasma Master File (hereinafter referred to as PMF) been issued or submitted for issuance, being used for this MAA:

☐ no ☐ yes

If yes:

Substance referring to PMF			
Function	API	EX[1]	P[2]
Name of the PMF Certificate Holder/ PMF Applicant			
Reference number of Application/Certificate			
Date of submission (if pending)			
Date of approval or last update (if approved)			

[1] EX=excipient (incl. starting materials used in the manufacture of the active substance/excipient).
[2] R=reagent/culture medium (incl. those used in the preparation of master and working cell banks).

3.6.4. Does the medicinal product contain or consist of Genetically Modified Organisms (GMOs):

☐ no ☐ yes

If yes, does the product comply established requirements:

☐ no ☐ yes

Provide necessary reference.

4. Other information

4.1. Are the intellectual rights for a medicinal product protected by patents effective within the Eurasian Economic Union Member State:

☐ no ☐ yes

If yes, please provide the following information:

Patent number	Effective within the Member State	Date of issuance	Effective by	Patent holder

For granting a marketing authorization for medicinal products (bringing a marketing authorization dossier of a medicinal product into compliance with the legal acts which constitute the law of the Eurasian Economic Union) having a patent issued in accordance with the Eurasian Economic Union Member State legislation, the applicant shall apply a certified copy of that patent or license agreement authorizing manufacturing or marketing an authorized medicinal product. Applicants shall provide a letter declaring that the intellectual rights of a third parties protected by the patent or transferred in accordance with the license are not violated due to the marketing authorization.

4.2. Has a trademark been approved in the Eurasian Economic Union Member States:

☐ no ☐ yes

If yes, please provide the following information:

Certificate number	Effective within the Member State	Date of issuance	Effective by	Certificate holder

A certified copy of the trademark certificate effective within the Eurasian Economic Union Member State shall be provided.

Where the applicant differs from the certificate holder, a copy of the license agreement certified by the applicant or a confirmation of a franchise for the trademark.

4.3. Has the manufacturer's country granted an authorization for the same medicinal product:

☐ no ☐ yes

Is there another countries where an authorization is granted for the same product:

☐ no ☐ yes

4.4. Was there scientific advice(s) given by Eurasian Economic Union Member States for this medicinal product:

☐ no ☐ yes

If yes:

Member State	
Date	
Reference of the scientific advice	

Was there scientific advice(s) given by the Expert Committee for medicinal products for this medicinal product:

☐ no ☐ yes

If yes:

Date	
Reference of the scientific advice	

4.5. Information on whether an authorization was refused/ suspended/ revoked manufacturer's country or other countries for the same product.

If yes:

Type of restriction	Reason	Country	Period	Date
…				

5. Appendices to the application

5.1. A letter for authorization for taking legal actions on behalf of the marketing authorization holder, if appropriate.

5.2. A copy the document confirming orphan designation for a medicinal product.

5.3. Copies of patents for the applied medicinal product effective within Eurasian Economic Union Member State.

5.4. Written confirmation that the intellectual rights of a third parties protected by the patent or transferred in accordance with the license are not violated due to the marketing authorization.

5.5. A certified copy of the trademark certificate effective within the Eurasian Economic Union Member State.

5.6. A declaration(s) from the Qualified Person of the manufacturing authorization holder that each manufacturing site where the medicinal product and active substance is manufactured including testing sites is in compliance the Rules of the Good Manufacturing Practice of the Eurasian Economic Union subject to approval by the Commission and guidelines of good manufacturing practice for starting materials.

III. APPLICATION FOR A VARIATION TO A MARKETING AUTHORIZATION FOR A MEDICINAL PRODUCT

The date the application received № _____
«___» _____ 20__ г.

Brand names of a medicinal product	
Active substances	
Strengths and	
Dosage form	
Presentation	
Marketing authorization holder	
Applicant	
Applicant's representative	
Marketing authorization data	
Number of a certificate of a marketing authorization	
Date of granting a marketing authorization	
Normative document number	

It is hereby confirmed that information in documents and particulars of the marketing authorization application dossier is reliable.
It is hereby confirmed that in case of failure to submit documents and particulars of the marketing authorization application dossier in response of observations of the competent authority (assessment organization) of the reference Member State within a maximum of 30 days, evaluation of the application shall be refused.
It is hereby confirmed that all existing marketing authorization application dossier data have been obtained in accordance with applicable legislation and that such data does not violate intellectual rights of a third party (subsections 5.3 and 5.4 of the Appendix to this application).
It is hereby confirmed that fees will be paid/have been paid according to the rules.

A letter for authorization for taking legal actions on behalf of the marketing authorization holder is provided (subsection 5.1 of the Appendix to this application).

On behalf of the applicant

_____
(signature)

_____
(name)

_____
(title)

SEAL

1. Common sections of the application

1.1. This application is submitted in accordance with the following.

1.1.1. The application is submitted under the mutual recognition procedure:

Reference Member State	
Brand name in the reference Member State	
Date of granting a marketing authorization	
Number of a certificate of a marketing authorization	
Copy of a certificate of a marketing authorization	
Application number	
Other Eurasian Economic Union Member States for application (where appropriate)	
Brand names in Member States concerned (where differ from that approved in the reference Member State)	

1.1.2. The application is submitted under the decentralized procedure:

Application number	
Reference Member State	
Brand name in the reference Member State	
Member States concerned for application submission	
Brand names in Member States concerned (where differ from that approved in the reference Member State)	

Note: This section shall be completed for each application including those referenced in this section.

2. Variations

№	Variation name	Variation type	Brief description of the variation
…			

When an application for the appropriate medicinal product type is submitted, other sections of the application on other medicinal product types shall not be completed.

☐ ORIGINAL MEDICINAL PRODUCT

☐ biological medicinal product	☐ other medicinal product
☐ new active substance (hereinafter referred to as API) Note: No information on API in the Common Register of the Authorized Medicinal Products of the Eurasian Economic Union or in the appropriate national registers Eurasian Economic Union Member States.	
☐ known API Note: There is information on AS in the Common Register of the Authorized Medicinal Products of the Eurasian Economic Union or in the appropriate national registers Eurasian Economic Union Member States.	

☐ GENERIC MEDICINAL PRODUCT

☐ one API ☐ more than one API

Original medicinal product:	
Name of the medicinal product, strength, dosage form	
Marketing authorization holder (company holding marketing authorization), date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the original medicinal product has been authorized	
Reference medicinal product used in equivalence studies (where conducted):	
Name of the medicinal product, strength, dosage form	
Marketing authorization holder (company holding marketing authorization), date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the reference medicinal product has been authorized	
Justification for using reference product where it differs from original product shall be supplied	
Any Expert Committee on medicinal products recommendations for a reference medicinal product selection	

Note: The section shall be completed for each medicinal product used in equivalence studies.

☐ SIMILAR BIOLIGICAL MEDICINAL PRODUCT (BIOSIMILAR)

Original biological medicinal product:

Name of the medicinal product, strength, dosage form	
Marketing authorization holder (company holding marketing authorization), date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the original medicinal product has been authorized	

Reference biological medicinal product:

Name of the medicinal product, strength, dosage form	
Marketing authorization holder, date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the reference medicinal product has been authorized	
Any Expert Committee on medicinal products recommendations for a reference medicinal product selection	
Differences with the reference biological medicinal product (as appropriate):	☐ different starting materials ☐ different manufacturing process ☐ different therapeutic indications ☐ different pharmaceutical form ☐ different strengths (qualitative difference in API) ☐ different route of administration ☐ other differences: _____ _____

☐ HYBRID MEDICINAL PRODUCT

Original medicinal product:	
Name of the medicinal product, strength, dosage form	
Marketing authorization holder, date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the original medicinal product has been authorized	
Differences with the original medicinal product:	☐ different active substance ☐ different pharmaceutical form ☐ different strengths (qualitative difference in AS) ☐ different route of administration ☐ different pharmacokinetics (including different bioavailability); ☐ differences in therapeutic indications ☐ other differences: _____

☐ COMBINATION MEDICINAL PRODUCT

☐ known combination ☐ new combination

Original medicinal product (in case of a known combination):

Name of the medicinal product, strength, dosage form	
Marketing authorization holder, date of granting a marketing authorization, number of a certificate of a marketing authorization, Eurasian Economic Union Member States where the original medicinal product has been authorized	

☐ WELL-ESTABLISHED MEDICINAL PRODUCT

☐ RADIOPHARMACEUTICAL OR PRECURSOR

☐ radiopharmaceutical kit

☐ radionuclide precursor

radionuclide source (primary or secondary) (where available)	
generator	

☐ HOMEOPATHIC MEDICINAL PRODUCT

☐ new homeopathic product not included in pharmacopoeias or monographs

☐ homeopathic product included in pharmacopoeias or monographs

☐ HERBAL MEDICINAL PRODUCT

☐ ORPHAN MEDICINAL PRODUCT

Has orphan designation been granted in the Eurasian Economic Union or elsewhere

☐ no ☐ pending ☐ yes

Date	
Number of a certificate of a marketing authorization for an orphan medicinal product	
Eurasian Economic Union Member States and/or other countries which have designated the medicinal product as orphan	

Orphan designation has been refused:

Date	
Decision number	
Application for designation has been withdrawn	
Date	
A copy of a document confirming orphan designation for a medicinal product (where available) (subsection 5.2 of Appendix to this application).	

3. Specific sections of the application

3.1. Name and ATC code	
3.1.1. Name of the medicinal product	
3.1.2. AS name or composition	

Note: only one name shall be given in the following order of priority: international nonproprietary name (hereinafter referred to as INN)*, name provided in the Pharmacopoeia of the Eurasian Economic Union or pharmacopoeias of Member States (or main pharmacopeias in accordance with the Eurasian Economic Union Member States Pharmacopeia Harmonization Conception), usual common name, scientific (chemical) name.

* The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant

3.1.3. Pharmacotherapeutic group

(Please use current ATC code)

ATC code	
Group	

If no ATC code has been assigned, please indicate if an application for ATC code has been made

3.2. Strength, pharmaceutical form, route of administration, container and pack sizes

3.2.1. Strength and Dosage form

(use current list of standard terms of the Eurasian Economic Union Pharmaceutical Form Nomenclature)

Dosage form	
Strengths	
3.2.2. Route of administration (use current list of standard terms of the Pharmaceutical Form Nomenclature)	
3.2.3. Container, closure and administration device(s), including description of material from which it is constructed (use current list of standard terms of the Pharmaceutical Form Nomenclature)	

For each packaging type please provide:
3.2.3.1. Package size (number of dosage units).
3.2.3.2. Proposed shelf life.
3.2.3.3. Proposed shelf life (after first opening container).
3.2.3.4. Proposed shelf life (after reconstitution or dilution).
3.2.3.5. Proposed storage conditions.
3.2.3.6. Proposed storage conditions after first opening of the container or intermediate packaging.

3.2.4. Information on delivery devices

3.3. Legal status

3.3.1. Proposed dispensing/classification:

☐ subject to medical prescription
☐ not subject to medical prescription
☐ in hospital settings

3.4. Marketing authorization holder

3.4.1. Marketing authorization holder:

Company name	
Address	
Country	
Telephone and telefax, where available	
E-Mail	

3.4.2. Marketing authorization holder representative (Person/company authorized for communication on behalf of the marketing authorization holder representative during the procedure, i.e. applicant):

Name	
Telephone and telefax, where available	
E-Mail	

When completing this section, a letter for authorization for taking legal actions on behalf of the marketing authorization holder shall be provided (Section 5.1 of the Appendix to this application).

3.4.3. Person/Company authorized for communication between the marketing authorization holder and the competent authorities after authorization if different from 3.4.2:

Name	
Company address	
Country	
Telephone and telefax, where available	
E-Mail	

When completing this section, a letter for authorization shall be provided (section 5.1 of the Appendix to this application).

3.4.4. The marketing authorization holder's qualified person responsible for pharmacovigilance in the Eurasian Economic Union Member States:

Name of the qualified person responsible for pharmacovigilance	
Company name (of the marketing authorization holder)	
Company address (of the marketing authorization holder)	
Country	
24 H Telephone and Telefax	
E-Mail	

Address where the marketing authorization holder's qualified person responsible for pharmacovigilance resides and lives.

Pharmacovigilance system master file: Number: Address:

3.4.5. The marketing authorization holder's qualified person responsible for pharmacovigilance in the Eurasian Economic Union Member States where differs from that referred to in section 3.4.4:

Name of the qualified person responsible for pharmacovigilance	
Company name (of the marketing authorization holder)	
Company address	
Country	
24 H Telephone and Telefax	
E-Mail	

Address where the marketing authorization holder's qualified person responsible for pharmacovigilance resides and lives.

3.5. Manufacturer

3.5.1. Authorized manufacturer responsible for batch release (as shown in the summary of product characteristics, package leaflet, and where applicable in the labelling)

Company name	
Address	
Country	
Telephone and telefax, where available	
E-Mail	

3.5.2. Manufacturer's quality control laboratory responsible for batch release for blood products and vaccines

Laboratory name	
Address	
Country	
Telephone and telefax, where available	
E-Mail	

3.5.3. Contact person in the Eurasian Economic Union (for each Member State, where appropriate) for product defects and recalls

Company name	
Address	
Country	
24 H Telephone and Telefax	
E-Mail	

3.5.4. Manufacturer of the medicinal product and sites of manufacture:

All manufacturing sites involved in manufacturing process of the medicinal product including solvents specifying the manufacturing step

Manufacturing step name*, company name*	
Address*	

Country*	
Telephone and telefax, where available*	
E-Mail*	

* For each site provide the relevant information (attach flow-chart indicating the sequence and activities of the different sites involved in the manufacturing process, including testing sites).

Has the site been inspected for compliance with the requirements of the Good Manufacturing Practice of the Eurasian Economic Union by the competent authority of the Eurasian Economic Union Member State:

☐ no ☐ yes

If yes, please provide:

Date of the latest inspection	
Competent authority name which carried out the inspection	
Inspection type	
Type of medicinal products and APIs inspected	
Conclusion	compliant: ☐ no ☐ yes

Has the site been inspected for compliance with the requirements of the Good Manufacturing Practice by the other country's competent authority (organization):

☐ no ☐ yes

If yes, please provide:

The date of the latest inspection	
Competent authority name which carried out the inspection	
Inspection type	
Type of medicinal products and APIs inspected	
Conclusion	compliant: ☐ no ☐ yes

3.5.5. Manufacturer of the API and sites of manufacture

All manufacturing sites involved in the manufacturing process of each AS specifying the manufacturing step. For biotech products include all sites of storage of master and working cell bank and preparation of working cell banks:

Manufacturing step name, active substance	
Company name, name of the entrepreneur	
Address	
Country	
Telephone and telefax, where available	
E-Mail	

For each active substance, attach a Qualified Person declaration in accordance with section 5.5 of the Appendix to this application (attach flow-chart indicating the sequence and activities of the different sites involved in the manufacturing process, including testing sites).

Has the API site been inspected for compliance with the requirements of the Rules of the Good

Manufacturing Practice of the Eurasian Economic Union by the competent authority of the Eurasian Economic Union Member State:

☐ no ☐ yes

Has a Ph.Eur. Certificate of suitability been issued for the API:

☐ no ☐ yes

If yes:

Active substance name	
Company name or name of the entrepreneur (manufacturer)	
CEP number	
Date of last update	

Has the API site been inspected for compliance with the requirements of the Good Manufacturing Practice by the other country's competent authority (organization):

☐ no ☐ yes

If yes, please provide:

Date of the latest inspection	
Competent authority name which carried out the inspection	
Inspection type	
Compliance document number	
Conclusion	compliant: ☐ no ☐ yes

Is an Active Substance Master File to be used for the active substance:

☐ no ☐ yes

If yes:

Active substance name	
Name of the Active Substance Master File holder	
Name of the API manufacturer if different from the Active Substance Master File holder	
Date of last update	

Is a certificate for a Vaccine Antigen Master File (hereinafter referred to as VAMF) been issued or submitted for issuance, being used for this MAA:

☐ no ☐ yes

If yes:

Vaccine antigen name	
Vaccine antigen manufacturer's/VAMF certificate holder's name	
Reference number of Application/Certificate	
Date of submission (if pending)	

Date of approval or last update	

3.5.6. Contract companies used for clinical trial(s) on bioavailability or bioequivalence or used for the validation of blood product manufacturing processes

For each contract company, state where analytical tests are performed and where clinical data are collected and give:

Title of the study	
Protocol code	
EudraCT-Number, if appropriate	
ClinicalTrials.gov-number, if appropriate	
Name of the contract research organization	
Address	
Telephone and telefax, where available	
E-Mail	

3.6. Qualitative and quantitative composition of the medicinal product

3.6.1. Qualitative and Quantitative composition in terms of the active substance and the excipients of the medicinal product

A note should be given as to which quantity the composition refers (e.g. per unit, per unit-volume, per unit-mass, etc.).
List the API separately from the excipients:

№	API name	Quantity (mass, volume, or potency units)	Unit	Reference/Monograph standard	Стать (моногра
№	Excipient name	Quantity (mass, volume, or potency units)	Unit	Reference/Monograph standard	Стать (моногра

Note: only one name shall be given in the following order of priority: INN**, name provided in the Pharmacopoeia of the Eurasian Economic Union or pharmacopoeias of Member States (or main pharmacopeias in accordance with the Eurasian Economic Union Member States Pharmacopeia Harmonization Conception), usual common name, scientific (chemical) name.

** The active substance should be declared by its recommended INN, accompanied by its salt or hydrate form if relevant.

Details of any overages should not be included in the formulation columns but stated below:

Active substances	
Excipient(s)	

3.6.2. List of materials of animal and/or human origin contained or used in the manufacturing process of the medicinal product

☐ NONE

Name	Function			Animal origin susceptible to TSE[3]	Other animal origin	Human origin	Ph.Eur. certificate of suitability for TSE[3] (where available)
	API	EX[1]	P[2]				
1							
2							
3							
....							

Specify whether a TSE Certificate of Suitability to the monograph of the European Pharmacopoeia or a document issued by the competent authority for animal health of the county of substance origin (based on clinical and laboratory control) on TSE[3] cases.

[1] EX=excipient (incl. starting materials used in the manufacture of the active substance/excipient).
[2] R=reagent/culture medium (incl. those used in the preparation of master and working cell banks).
[3] TSE=transmissible spongiform encephalopathy.

3.6.3. Is a certificate for a Plasma Master File (hereinafter referred to as PMF) been issued or submitted for issuance, being used for this MAA:

☐ no ☐ yes

If yes:

Substance referring to PMF			
Function	API	EX[1]	P[2]
Name of the PMF Certificate Holder/ PMF Applicant			
Reference number of Application/Certificate			
Date of submission (if pending)			
Date of approval or last update (if approved)			

[1] EX=excipient (incl. starting materials used in the manufacture of the active substance/excipient).
[2] R=reagent/culture medium (incl. those used in the preparation of master and working cell banks).

3.6.4. Does the medicinal product contain or consist of Genetically Modified Organisms (GMOs):

☐ no ☐ yes

If yes, does the product comply established requirements:

☐ no ☐ yes

Provide necessary reference.

4. Other information

4.1. Are the intellectual rights for a medicinal product protected by patents effective within the Eurasian Economic Union Member State:

☐ no ☐ yes

If yes, please provide the following information:

Patent number	Effective within the Member State	Date of issuance	Effective by	Patent holder

For granting a marketing authorization for medicinal products (bringing a marketing authorization dossier of a medicinal product into compliance with the legal acts which constitute the law of the Eurasian Economic Union) having a patent issued in accordance with the Eurasian Economic Union Member State legislation, the applicant shall apply a certified copy of that patent or license agreement authorizing manufacturing or marketing an authorized medicinal product. Applicants shall provide a letter declaring that the intellectual rights of a third parties protected by the patent or transferred in accordance with the license are not violated due to the marketing authorization.

4.2. Has a trademark been approved in the Eurasian Economic Union Member States:

☐ no ☐ yes

If yes, please provide the following information:

Certificate number	Effective within the Member State	Date of issuance	Effective by	Certificate holder

A certified copy of the trademark certificate effective within the Eurasian Economic Union Member State shall be provided.

Where the applicant differs from the certificate holder, a copy of the license agreement certified by the applicant or a confirmation of a franchise for the trademark.

4.3. Has the manufacturer's country granted an authorization for the same medicinal product:

☐ no ☐ yes

Is there another countries where an authorization is granted for the same product:

☐ no ☐ yes

4.4. Was there scientific advice(s) given by Eurasian Economic Union Member States for this medicinal product:

☐ no ☐ yes

If yes:

Eurasian Economic Union Member State	
Date	
Reference of the scientific advice	

Was there scientific advice(s) given by the Expert Committee for medicinal products for this medicinal product:

☐ no ☐ yes

If yes:

Date	
Reference of the scientific advice	

4.5. Information on whether an authorization was refused/ suspended/ revoked manufacturer's country or other countries for the same product.

If yes:

Type of restriction	Reason	Country	Period	Date
…				

5. Appendices to the application

5.1. A letter for authorization for taking legal actions on behalf of the marketing authorization holder, if appropriate.

5.2. A copy the document confirming orphan designation for a medicinal product.

5.3. Copies of patents for the applied medicinal product effective within Eurasian Economic Union Member State.

5.4. Written confirmation that the intellectual rights of a third parties protected by the patent or transferred in accordance with the license are not violated due to the marketing authorization.

5.5. A certified copy of the trademark certificate effective within the Eurasian Economic Union Member State.

5.6. A declaration(s) from the Qualified Person of the manufacturing authorization holder that each manufacturing site where the medicinal product and active substance is manufactured including testing sites is in compliance the Rules of the Good Manufacturing Practice of the Eurasian Economic Union subject to approval by the Commission and guidelines of good manufacturing practice for starting materials.

APPENDIX 3
to the Rules of authorization and
assessment of medicinal products
for human use

GUIDANCE
on drafting a normative document accompanying an application for a marketing authorization

The draft normative document (hereinafter referred to as ND) shall include following 8 sections:

1. Title page including:

- Medicinal product name (Brand name and INN; where no INN exist, the usual common name; where no usual common name exist, chemical name);
- Dosage form
- Strength(s)
- Marketing authorization holder's name and countries;
- Space for ND number (to be specified as a number of a certificate of a marketing authorization issued by the reference Member State and the authorization date in DD.MM.YYYY format using dash);
- 'approved' mark.

2. Composition of the finished medicinal product shall correspond to 3.2.P.5.1 of Module 3 (functions not needed) and shall be provided in a separate section of the ND in the form qualitative and quantitative composition of active substances and excipients together with references to pharmacopoeias or quality standards.

3. Specification (in accordance with 3.2.P.5.1 of Module 3) in tabular format containing three following columns:

- A list of all tests;
- Acceptance criteria;
- References to test procedures.

Tests shall be established in accordance with requirement of general chapters/monographs of the Pharmacopoeia of the Eurasian Economic Union (hereinafter referred to as the Union) for dosage forms taking into account particular pharmaceutical form of the finished medicinal product depending on nature of the active substance and in accordance with this document.

Name of tests in the specification shall be in accordance with the Pharmacopoeia of the Eurasian Economic Union.

Where the test is carried out periodically, periodicity shall be established in the specification.

4. Detailed description of test procedures of the finished product for all specification tests together with references to the Union Pharmacopoeia (as appropriate) in accordance with 3.2.P.5.2 of Module 3

5. In the *Packaging* section of the ND, the description of the container (ampoules, vials, jars, pouch, etc.), pack size (e.g. number of tablets in a blister), intermediate packaging, outer (user) packaging and number of containers in it (e.g. number of blisters), desiccant, patient leaflet (medication guide), other components (a needle, dropper, clip, etc.), etc.

6. In the *Labeling* section of the ND, the reference on Module 1, section 1.3.2 shall be provided.

7. Storage conditions

8. Shelf-life (expiry date)

APPENDIX 4
to the Rules of authorization and
assessment of medicinal products
for human use

REQUIREMENTS
for a marketing authorization application dossier in the Common Technical Document (CTD) format

I. LIST OF THE DOCUMENTS AT THE MODULES OF MARKETING AUTHORIZATION APPLICATION DOSSIER

MODULE 1: ADMINISTRATIVE INFORMATION

1.0. Cover letter (as in CTD)

1.1. Table of Contents

1.2. General documentation

1.2.1. Application for marketing authorization for a medicinal product

1.2.2. Documents confirming the payment of a fee (duty) the assessment of, and for the granting a marketing authorization for, a medicinal product in accordance with the legislation of Eurasian Economic Union Member State which is to grant a marketing authorization

1.2.3. A copy of the Certificate of Pharmaceutical Product complying with the WHO recommendations (properly certified) and issued by the competent authority of the manufacturer's own country. In the absence of such a certificate, the document (properly certified) that confirms a marketing authorization of a medicinal product in the manufacturer's own country and/or in the marketing authorization holder's own country where appropriate.

1.2.4. Translated into Russian and properly certified copy of the competent authority's assessment report on a marketing authorization in the manufacturer's own country or marketing authorization holder's own country (where available).

1.2.5. A conclusion (recommendation) of the competent authority (assessment organization) of the Member State drawn up based on the outcome of the preliminary scientific advice on the medicinal product in the Member State(s) (where available).

1.2.6. The recommendation of the Expert Committee for Medicinal Products at the Eurasian Economic Commission (hereinafter referred to in as Commission) drawn up based on the outcome of the preliminary scientific advice on the medicinal product (where available).

1.3. Summary of Product Characteristics, package leaflet (Patient Leaflet), labelling

1.3.1. Draft summary of product characteristics, medication guide (patient leaflet) drawn up in Russian in accordance with the requirements laid down by the bodies of the Eurasian Economic Union.

1.3.2. Mock-ups of the outer (user), immediate (inner), and intermediate packaging drawn up in Russian in accordance with the requirements laid down by the bodies of the Eurasian Economic Union.

1.3.3. Consultation with Target Patient Groups on the wording of package leaflet (patient leaflet) (where available)

1.3.4. Copies of summary of product characteristics and medication guide (patient leaflet) approved by the competent authority of the manufacturer's own country and/or marketing authorization holder's own country and/or other country with strong pharmaceutical regulation together with the latest revision date certified by the marketing authorization holder (where available).

1.4. Information on regulatory status of a medicinal product in other countries, where appropriate

1.4.1. The list of countries where the medicinal product has been applied for granting a marketing authorization, authorized for marketing, where granting of a marketing authorization has been refused or suspended together with the number and the date of marketing authorization, the period of its validity or the date of decision to refuse granting of a marketing authorization, to suspend a marketing authorization; the information provided shall be certified by the marketing authorization holder.

1.5. Quality documents

1.5.1. Transmissible Spongiform Encephalopathy Certificate of Suitability to the monograph of the Pharmacopoeia of the Eurasian Economic Union or European Pharmacopoeia or a document issued by the competent authority for animal health of the county of origin where substances of animal origin are used, where appropriate.

1.5.2. The letter of the active substance master file holder committing to inform the manufacturer of the finished product and competent authority of the Eurasian Economic Union Member State on any modification before any significant amendments are made to the active substance master file (a certified copy of the letter signed of the qualified person certifying the quality of translation)

1.5.3. The active substance master file holder's permission to the competent authority to assess the data in the active substance master file upon request of the competent authority of the Eurasian Economic Union Member State (the Letter of Access)

1.5.4. Copy of a Certificate of Suitability to the monograph of the European Pharmacopoeia (where available).

1.5.5. Copy of a Plasma Master File Certificate issued by the competent authority of the manufacturer's own country (where available).

1.5.6. Copy of a Vaccine Antigen Master File issued by the competent authority of the manufacturer's own country (where available).

1.6. Manufacturing process documents

1.6.1. Properly certified copy of a valid document issued by the competent authority of the Eurasian Economic Union Member State, certifying compliance of the manufacturer (manufacturing site) of a medicinal product applied for granting a marketing authorization with the Requirements of the Eurasian Economic Union Good Manufacturing Practice subject to approval by the Eurasian Economic Commission.

Properly certified copies of valid documents issued by the competent authorities of the country or countries where manufacturing site or manufacturing sites of different manufacturing steps is/are located and/or other competent authority or web-site of the Register of GMP certificates issued by the competent authorities (e.g. EudraGMDP) (where applicable), certifying compliance of the manufacturer with the Good Manufacturing Practice, where appropriate.

1.6.2. Properly certified copies of a valid manufacturer's license (together with annexes) issued by the competent authority of the country where manufacturing site or manufacturing sites of different manufacturing steps are located

1.6.3. Properly certified copy of a manufacturing site(s) inspection report(s) on compliance with GMP carried out by the competent authority of a manufacturer's own country or other

competent authority within previous 3 years together with a report on corrective actions and preventative actions (CAPA) taken following the inspection (where available) (where available)

1.6.4. Properly certified copy of an agreement between a medicinal product marketing authorization holder and a medicinal product manufacturer on GMP compliance issues where the medicinal product marketing authorization holder is not involved in manufacturing of the medicinal product (where available)

1.6.5. Properly certified copy of an agreement between a contract manufacturing site and a manufacturer on GMP compliance issues where the whole manufacturing process or any step of the manufacturing process is carried out on contract manufacturing site (where applicable)

1.6.6. Information on any regulatory action taken by the competent authority within previous 3 years beginning with the application date, based on the outcome of a manufacturing site inspection (where available)

1.6.7. A qualified person letter certifying compliance of the manufacturing of a medicinal product applied for marketing authorization with the Requirements of the Rules of the Good Manufacturing Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission including starting materials at each manufacturing site involved in the manufacturing of the finished product and of the active substance including sites where release testing or in-process testing is carried out. The letter shall be signed by the qualified person and certified by the manufacturer’s seal and accompanied by the translation into Russian where necessary.

1.6.8. Information on product quality related complaints if those products have been manufactured by the manufacturing site where medicinal product applied for marketing authorization is to be manufactured, gathered within previous 3 years, where appropriate.

1.6.9. The consent to be a subject of a pharmaceutical inspection for compliance with the requirements of the Rules of the Good Manufacturing Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission

1.6.10. A copy of manufacturing site(s) master file certified by the applicant (where applicable).

1.6.11. The description of the finished product and active substance manufacturing process steps reflecting all manufacturing sites including testing sites.

1.7. Information about the Experts

1.7.1. Information (brief summary) about the Quality Expert

1.7.2. Information (brief summary) about the Non-clinical Expert

1.7.3. Information (brief summary) about the Clinical Expert

1.8. Specific requirements for Different Types of Applications

1.8.1. A letter of a marketing authorization holder on an additional brand name of a medicinal product, where applicable

1.8.2. Information relating to Clinical Trials, where applicable

1.8.3. Tabulated list of clinical trials, where applicable

1.8.4. A letter of a marketing authorization holder on compliance of clinical trials of a medicinal product applied for a marketing authorization with the requirements of the Rules of the Good Clinical Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission

1.9. Applicant’s documentation for the environmental risk assessment (where available)

1.9.1. A letter of an applicant notifying that medicinal products contain or produced from genetically modified organisms (where applicable).

1.10. Information relating to applicant's pharmacovigilance activities in a Eurasian Economic Union Member State

1.10.1. Marketing authorization holder's pharmacovigilance system master file drawn up in accordance with the Good Pharmacovigilance Practice of the Eurasian Economic Union and a brief description of a marketing authorization holder' pharmacovigilance system

1.10.2. A written confirmation by the marketing authorization holder that there is a qualified person responsible for pharmacovigilance at his disposal within a Eurasian Economic Union Member State

1.10.3. The Risk Management Plan for a medicinal product applied for a marketing authorization drawn up in accordance with the requirement of the Rules of the Good Pharmacovigilance Practice of the Union. The Risk Management Plan may be submitted electronically together with its summary in paper format (where applicable)

1.10.4. Properly certified written confirmation that more than one legal persons will respect all obligations of a marketing authorization holder where marketing authorization for a medicinal product was granted to different legal entities (where applicable).

1.11. Copies of documents confirming the trademark registration (where applicable)

MODULE 2: SUMMARIES OF COMMON TECHNICAL DOCUMENT

2.1. Table of contents of Modules 2 to 5

2.2. Introduction to CTD

2.3. Quality overall summary

2.4. Non-clinical overview

2.5. Clinical overview

2.6. Non-clinical summary

2.6.1. Pharmacology Written Summary

2.6.2. Pharmacology Tabulated Summary

2.6.3. Pharmacokinetics Written Summary

2.6.4. Pharmacokinetics Tabulated Summary

2.6.5. Toxicology Written Summary

2.6.6. Toxicology Tabulated Summary.

2.7. Clinical Summary

2.7.1. Summary of Biopharmaceutics and Associated Analytical Methods

2.7.2. Summary of Clinical Pharmacology Studies

2.7.3. Summary of Clinical Efficacy

2.7.4. Summary of Clinical Safety

2.7.5. Copies of literature references used

2.7.6. Synopses of Individual Studies

MODULE 3: QUALITY

3.1. Table of contents of Module 3

3.2. Basic principles and requirements

3.2.S. Active substance (API); for medicinal products containing more than one active substance, the full information shall be provided for each substance**

3.2.S.1. General information and information related to the starting and raw materials**

3.2.S.1.1 Nomenclature of the API**

3.2.S.1.2 Structure of the API **

3.2.S.1.3 General Properties of the API **

3.2.S.2. Manufacturing process of the active substance

3.2.S.2.1 Manufacturer**

3.2.S.2.2 Description of Manufacturing Process and Process Controls

3.2.S.2.3 Control of Materials

3.2.S.2.4 Controls of Critical Steps and Intermediates

3.2.S.2.5 Process Validation and/or Evaluation

3.2.S.2.6 Manufacturing Process Development

3.2.S.3. Characterization of the API**

3.2.S.3.1 Elucidation of Structure and other Characteristics

3.2.S.3.2 Impurities**

3.2.S.4 Control of the API**

3.2.S.4.1 Specification**

3.2.S.4.2 Analytical Procedures**

3.2.S.4.3 Validation of Analytical Procedures

3.2.S.4.4 Batch Analyses**

3.2.S.4.5 Justification of Specification

3.2.S.5 Reference Standards or Materials

3.2.S.6 Container Closure System**

3.2.S.7. Stability**

3.2.S.7.1 Stability Summary and Conclusions**

3.2.S.7.2 Post-approval Stability Protocol and Stability Commitment**

3.2.S.7.3 Stability Data**

3.2.P. Finished medicinal product

3.2.P.1. Description and composition of the finished medicinal product

3.2.P.2. Pharmaceutical development

3.2.P.2.1 Components of the Finished Medicinal Product

3.2.P.2.1.1 Active Substance

3.2.P.2.1.2 Excipients

3.2.P.2.2 Finished Medicinal Product

3.2.P.2.2.1 Formulation Development

3.2.P.2.2.2 Overages

3.2.P.2.2.3 Physicochemical and Biological Properties

3.2.P.2.3 Manufacturing Process Development

3.2.P.2.4 Container Closure System

3.2.P.2.5 Microbiological Attributes

3.2.P.2.6 Compatibility

3.2.P.3 Manufacture of the Finished Medicinal Product

3.2.P.3.1 Manufacturers

3.2.P.3.2 Batch Formula

3.2.P.3.3 Description of Manufacturing Process and Process Controls

3.2.P.3.4 Controls of Critical Steps and Intermediates

3.2.P.3.5 Process Validation and/or Evaluation

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

3.2.P.4.2 Analytical Procedures

3.2.P.4.3 Validation of Analytical Procedures

3.2.P.4.4 Justification of Specifications

3.2.P.4.5 Excipients of Human or Animal Origin

3.2.P.4.6 Novel Excipients

3.2.P.5 Control of Drug Product

3.2.P.5.1 Specifications

3.2.P.5.2 Analytical Procedures. A draft normative document drawn up in accordance with recommendations subject to approval by the Eurasian Economic Commission***

3.2.P.5.3 Validation of Analytical Procedures

3.2.P.5.4 Batch Analyses

3.2.P.5.5 Characterization of Impurities

3.2.P.5.6 Justification of Specifications

3.2.P.6 Reference Standards or Materials

3.2.P.7 Container Closure System

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion**

3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment

3.2.P.8.3 Stability Data

3.2.A Appendices

3.2.A.1 Facilities and Equipment

3.2.A.2 Adventitious Agents Safety Evaluation

3.2.A.3 Excipients

3.2.R Regional Information

3.3. Literature References

MODULE 4: NON-CLINICAL (PRECLINICAL) REPORTS

4.1. Table of Content of Module 4

4.2 Study reports (where appropriate)

4.2.1 Pharmacology

4.2.1.1 Primary Pharmacodynamics

4.2.1.2 Secondary Pharmacodynamics

4.2.1.3 Safety Pharmacology

4.2.1.4 Pharmacodynamic Drug Interactions

4.2.2 Pharmacokinetics

4.2.2.1 Analytical Methods and Validation Reports (if separate reports are available)

4.2.2.2 Absorption
4.2.2.3 Distribution
4.2.2.4 Metabolism
4.2.2.5 Excretion

4.2.2.6 Pharmacokinetic Drug Interactions (nonclinical)
4.2.2.7 Other Pharmacokinetic Studies

4.2.3 Toxicology
4.2.3.1 Single-Dose Toxicity (in order by species, by route)

4.2.3.2 Repeat-Dose Toxicity (in order by species, by route, by duration; including supportive toxicokinetics evaluations)

4.2.3.3 Genotoxicity

4.2.3.4 Carcinogenicity

4.2.3.5 Reproductive and Developmental Toxicity: fertility and early embryonic development, embryo-fetal development, prenatal and postnatal development, studies in which the offspring (juvenile animals) are dosed and/or further evaluated

4.2.3.6 Local Tolerance
4.2.3.7 Other Toxicity Studies: antigenicity, immunotoxicity, mechanistic studies, dependence, metabolites, impurities, etc.

4.3. Literature References

MODULE 5: CLINICAL REPORTS

5.1 Table of Contents of Module 5
5.2 Tabular Listing of All Clinical Studies
5.3 Clinical Study Reports

5.3.1 Reports of Biopharmaceutic Studies

5.3.2 Reports of Studies Pertinent to Pharmacokinetics using Human Biomaterials

5.3.3 Reports of Human Pharmacokinetic (PK) Studies

5.3.4 Reports of Human Pharmacodynamic (PD) Studies

5.3.5 Reports of Efficacy and Safety Studies

5.3.6 Reports of Post-Marketing Experience

5.3.7 Case Report Forms and Individual Patient Listings

5.4 Literature References

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* Documents shall be provided unless the Member State legislation prohibits requesting documents which are in possession of or might be retrieved by a Member State independently.

** Minimal extent of information to be supplemented in the Module 3.2.S. In case particular documents omitted, a justification shall be provided in the appropriate section. For products of animal origin, Module 3.2 shall contain the following additional information: species, age and diet of source animals, source tissue nature (category) from the perspective of prion safety, manufacturing process description specifying extraction solvents and process parameters, quality control of source materials including prion detection methods in the finished product, where necessary.

*** Until the recommendations of the Eurasian Economic Commission adopted, a draft normative document for a medicinal product shall be drawn up in accordance with guidelines of reference Member State.

Note:

Unless in the Rules of authorization and assessment of medicinal products for human use subject to approval by the Eurasian Economic Commission otherwise specified, documents shall be certified by the applicant. Documents of a marketing authorization application dossier shall be drawn in Russian in accordance with the provisions of Part II of this document. The Module 1.6.3 document and Modules 3 to 5 documents may be provided in English together with mandatory Russian versions of the following section of Module 3: 3.2.S.2.2 Description of Manufacturing Process and Process Controls, 3.2.S.2.5 Process Validation and/or Evaluation, 3.2.S.3.2 Impurities, 3.2.S.4.2 Analytical Procedures, 3.2.S.4.3 Validation of Analytical Procedures, 3.2.S.4.5 Justification of Specification, 3.2.S.7.1 Stability Summary and Conclusions, 3.2.P.1. Description and composition of the finished medicinal product, 3.2.P.2.2.1 Formulation Development, 3.2.P.2.2.2 Overages, 3.2.P.2.2.3 Physicochemical and Biological Properties, 3.2.P.2.4 Container Closure System, 3.2.P.2.6 Compatibility, 3.2.P.3.3 Description of Manufacturing Process and Process Controls, 3.2.P.3.4 Controls of Critical Steps and Intermediates, 3.2.P.3.5 Process Validation and/or Evaluation, 3.2.P.4.3 Validation of Analytical Procedures, 3.2.P.4.4 Justification of Specifications, 3.2.P.4.5 Excipients of Human or Animal Origin, 3.2.P.4.6 Novel Excipients, 3.2.P.5.1 Specifications, 3.2.P.5.2 Analytical Procedures, 3.2.P.5.3 Validation of Analytical Procedures, 3.2.P.5.5 Characterization of Impurities, 3.2.P.5.6 Justification of Specifications, 3.2.P.7 Container Closure System, 3.2.P.8.1 Stability Summary and Conclusion, 3.2.P.8.2 Post-approval Stability Protocol and Stability Commitment, 3.2.A.2 Adventitious Agents Safety Evaluation, 3.2.A.3 Excipients. The English version Pharmacovigilance Master File is accepted together with Russian version of the brief description of marketing authorization holder’s pharmacovigilance system, the English version of a Risk Management Plan together with its Russian version.

II. APPROXIMATE LIST OF DOCUMENTS TO BE INCLUDED IN A MARKETING AUTHORIZATION APPLICATION DOSSIER FOR DIFFERENT MEDICINAL PRODUCTS TYPES

This List is supplementary for Part I of this Document; it contains tabular description of approximate contents of a marketing authorization application dossier for different medicinal products types.

When preparing and validating the marketing authorization application dossier provisions of Part I of this document and Appendix 1 to the Rules of authorization and assessment of medicinal products for human use subject to approval by the Eurasian Economic Commission, as well shall be followed primarily, as well as the extent of non-clinical and clinical studies prescribed by the Rules of conducting bioequivalence studies of medicinal products in the Eurasian Economic Union and the Rules of conducting studies of biological medicinal products in the Eurasian Economic Union subject to approval by the Eurasian Economic Commission.

Module section number	Medicinal product								
	original	generic	hybrid	biosimilar	vaccines (sera)	homeopathic	homeopathic (simplified dossier)	herbal	herbal (simplified dossier)
MODULE 1: ADMINISTRATIVE INFORMATION									
1.0.	+	+	+	+	+	+	+	+	+
1.1.	+	+	+	+	+	+	+	+	+
1.2.									
1.2.1.	+	+	+	+	+	+	+	+	+
1.2.2.	+	+	+	+	+	+	+	+	+
1.2.3.	(+)	(+)	(+)	(+)	(+)	(+)	-	(+)	-
1.2.4	(+)	(+)	(+)	(+)	(+)	(+)	-	(+)	-
1.2.5.	(+)	(+)	(+)	(+)	(+)	(+)	-	(+)	-
1.2.6.	(+)	(+)	(+)	(+)	(+)	(+)	-	(+)	-
1.3.									
1.3.1.	+	+	+	+	+	+	+	+	+
1.3.2.	+	+	+	+	+	+	+	+	+
1.3.3.	(+)		(+)						
1.3.4.	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
1.4.									
1.4.1.	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
1.5.									
1.5.1.	+	+	+	+	+	+	+	+	+
1.5.2.	+	+	+	+	+	+	-	+	+
1.5.3.	+	+	+	+	+	-	-	-	-

Module section number	Medicinal product								
	original	generic	hybrid	biosimilar	vaccines (sera)	homeopathic	homeopathic (simplified dossier)	herbal	herbal (simplified dossier)
1.5.4.	(+)	(+)	(+)	(+)	(+)	(+)	-	(+)	(+)
1.5.5.	(+)	-	-	(+)	(+)	(+)	-	-	-
1.5.6.	(+)	-	-	(+)	(+)	-	-	-	-
1.6.									
1.6.1.	+	+	+	+	+	+	+	+	+
1.6.2.	+	+	+	+	+	+	+	+	+
1.6.3.	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
1.6.4.	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+/)
1.6.5.	+	+	+	+	+	+	+	+	+
1.6.6.	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
1.6.7.	+	+	+	+	+	+	+	+	+
1.6.8.	+	+	+	+	+	+	+	+	+
1.6.9.	+	+	+	+	+	+	+	+	+
1.6.10.	+	+	+	+	+	+	+	+	+
1.6.11.	+	+	+	+	+	+	+	+	+
1.7.									
1.7.1	+	+	+	+	+	+	+	+	+
1.7.2.	+	+	+	+	+	+	+	+	+
1.7.3.	+	+	+	+	+	+	+	+	+
1.8.									
1.8.1.	+	+	+	+	+	+	+	+	+
1.8.2.	+	+	+	+	+	+	-	+)	-

Module section number	Medicinal product								
	original	generic	hybrid	biosimilar	vaccines (sera)	homeopathic	homeopathic (simplified dossier)	herbal	herbal (simplified dossier)
1.8.3.	+	+	+	+	+	+	-	+	-
1.8.4.	+	+	+	+	+	+	-	+	-
1.9.									
1.9.1.	+	+	+	+	+	-	-	-	-
1.10.									
1.10.1.	+	+	+	+	+	+	+	+	+
1.10.2.	+	+	+	+	+	+	+	+	+
1.10.3.	+	-	+	+	+	-	-	-	-
1.10.4.	+	+	+	+	+	+	+	+	+
1.11.	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)
MODULE 2: SUMMARIES OF COMMON TECHNICAL DOCUMENT									
2.1.	+	+	+	+	+	+	+	+	+
2.2.	+	+	+	+	+	+	+	+	+
2.3.	+	+	+	+	+	+	+	+	+
2.4.	+	+	+	+	+	+	+	+	+
2.5.	+	+	+	+	+	+	+	+	+
2.6.									
2.6.1.	+	-	-	+	+	-	-	+	-
2.6.2.	+	-	-	+	+	-	-	+	-
2.6.3.	+	-	-	+	-	-	-	-	-
2.6.4.	+	-	-	+	-	-	-	-	-

Module section number	Medicinal product								
	original	generic	hybrid	biosimilar	vaccines (sera)	homeopathic	homeopathic (simplified dossier)	herbal	herbal (simplified dossier)
2.6.5.	+	-	-	+	+	+	-	+	-
2.6.6.	+	-	+	+	+	+	-	+	-
2.7.									
2.7.1.	+	+	+	+	-	-	-	+	-
2.7.2.	+	-	+	+	-	-	-	+	-
2.7.3.	+	-	-	+	+	+	-	+	-
2.7.4.	+	-	-	+	+	+	-	+	-
2.7.5.	+	+	+	+	+	+	+	+	+
2.7.6.	+	-	+	+	+	+	-	+	-
MODULE 3: QUALITY									
3.1.	+	+	+	+	+	+	+	+	+
3.2.	+	+	+	+	+	+	+	+	+
3.2.S.									
3.2.S.1.	+	+	+	+	+	+	+	+	+
3.2.S.2.	+	+	+	+	+	+	+	+	+
3.2.S.3.	+	+	+	+	+	+	+	+	+
3.2.S.4.	+	+	+	+	+	+	+	+	+
3.2.S.5.	+	+	+	+	+	+	-	+	+
3.2.S.6.	+	+	+	+	+	+	+	+	+
3.2.S.7.	+	+	+	+	+	+	+	+	+
3.2.P.									

Module section number	Medicinal product								
	original	generic	hybrid	biosimilar	vaccines (sera)	homeopathic	homeopathic (simplified dossier)	herbal	herbal (simplified dossier)
3.2.P.1.	+	+	+	+	+	+	+	+	+
3.2.P.2.	+	+	+	+	+	-	-	-	-
3.2.P.3.	+	+	+	+	+	+	+	+	+
3.2.P.4.	+	+	+	+	+	+	+	+	+
3.2.P.5.	+	+	+	+	+	+	+	+	+
3.2.P.6.									
3.2.P.7.	+	+	+	+	+	+	+	+	+
3.2.P.8.	+	+	+	+	+	+	+	+	+
3.2.A.	+	+	+	+	+	+	-	+	+
3.2.A.1.	+	+	+	+	+	+	-	+	+
3.2.A.2.	+	+	+	+	+	(+)	-	(+)	(+)
3.2.A.3.	+	+	+	+	+	(+)	-	(+)	(+)
3.2.R.	+	+	+	+	+	+	-	+	+
3.3.	+	+	+	+	+	+	+	+	+
MODULE 4: NON-CLINICAL (PRECLINICAL) REPORTS									
4.1.	+	+	+	+	+	+	-	+	-
4.2.									
4.2.1.	+	-	-	+	+	-	-	+	-
4.2.2.	+	-	-	+	-	-	-	-	-
4.2.3.	+	-	+	+	+	+	-	+	-
4.3.	+	+	+	+	+	+	-	+	+

Module section number	Medicinal product								
	original	generic	hybrid	biosimilar	vaccines (sera)	homeopathic	homeopathic (simplified dossier)	herbal	herbal (simplified dossier)
MODULE 5: CLINICAL REPORTS									
5.1.	+	+	+	+	+	+	-	+	-
5.2.	+	+	+	+	+	+	-	+	-
5.3.									
5.3.1.	+	+	+	+	-	-	-	+	-
5.3.2.	+	-	+	+	-	-	-	-	-
5.3.3.	+	-	+	+	-	-	-	-	-
5.3.4.	+	-	+	+	+	-	-	+	-
5.3.5.	+	-	-	+	+	+	-	+	-
5.3.6.	+	+	+	+	+	+	-	+	-
5.3.7.	+	+	+	+	+	+	-	+	-
5.4.	+	+	+	+	+	+	-	+	+

Note:
"+" – the document is provided in accordance with the instructions given in part 1 of this annex without fail or if necessary
"(+)" – if applicable
"-" – not nesessary

APPENDIX 5
to the Rules of authorization and
assessment of medicinal products
for human use

ORGANISATION
of the Common Technical Document for the marketing authorization of the medicinal products for human use

I. OBJECTIVE

This document presents the Eurasian Economic Union Member State (hereinafter referred to as Member States and Union, respectively) agreed upon common format for the preparation of a well-structured Common Technical Document (hereinafter referred to as CTD) for applications that will be submitted to competent authorities of the Member States.

A common format for the technical documentation will significantly reduce the time and resources needed to compile the marketing authorization application dossier of the medicinal products for human use and will ease the preparation of electronic submissions (hereinafter referred to as eCTD).

Regulatory assessment and communication with the applicant will be facilitated by a standard document of common elements. In addition, exchange of regulatory information between competent authorities of the Member States will be simplified.

II. SCOPE

This document primarily addresses the organization of the information to be presented in marketing authorization application dossier for new medicinal products (including biotechnological).

This document is not intended to indicate what studies are required. It merely indicates an appropriate format for the data that have been acquired. Applicants should not modify the overall organization of the CTD as outlined in the guideline. However, in the Nonclinical and Clinical Summaries, applicants can modify individual formats if needed to provide the best possible presentation of the technical information, in order to facilitate the understanding and evaluation of the results.

III. GENERAL PRINCIPLES

Throughout the CTD, the display of information should be unambiguous and transparent, in order to facilitate the assessment of the basic data and to help a expert become quickly oriented to the marketing authorization application dossier contents. Text and tables should be prepared using margins that allow the document to be printed on both A4 paper. The left-hand margin should be sufficiently large that information is not obscured by the method of binding (for example, the left margin 3 cm, the right margin 1.5 cm, top and bottom 2 cm). Font sizes for text and tables should be of a style and size that are large enough to be easily legible, even after photocopying. Times New Roman, 12-point font, is recommended for narrative text. Every page should be numbered, according to the granularity document. Acronyms and abbreviations should be defined the first time they are used in each module. References should be cited in accordance with the current edition of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, International Committee of Medical Journal Editors (ICMJE). (The first edition of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals was conceived by the Vancouver Group and was published in 1979.)

IV. ORGANIZATION OF THE COMMON TECHNICAL DOCUMENT

The CTD is organized into five modules. Module 1 is Member States specific. Modules 2, 3, 4, and 5 are intended to be common for all regions. Conformance with this guideline should ensure that these four modules are provided in a format acceptable to the competent authorities of the Member States.

Module 1. Administrative Information and Prescribing Information

This module should contain documents specific to each region; for example, application forms or the proposed label for use in the Member States. The content and format of this module specified in Appendix 1 to the Rules of authorization and assessment of medicinal products for human use (hereinafter referred to as the Rules).

Module 2. CTD Summaries

Module 2 should begin with a general introduction to the pharmaceutical, including its pharmacologic class, mode of action, and proposed clinical use. In general, the Introduction should not exceed one page.

Module 2 should contain 7 sections in the following order:

- CTD Table of Contents
- CTD Introduction
- Quality Overall Summary
- Nonclinical Overview
- Clinical Overview
- Nonclinical Written and Tabulated Summaries
- Clinical Summary

The description of these summaries is provided in Appendix 1 to the Rules.

Module 3. Quality

Information on Quality should be presented in the structured format described in Appendix 1 to the Rules.

Module 4. Nonclinical Study Reports

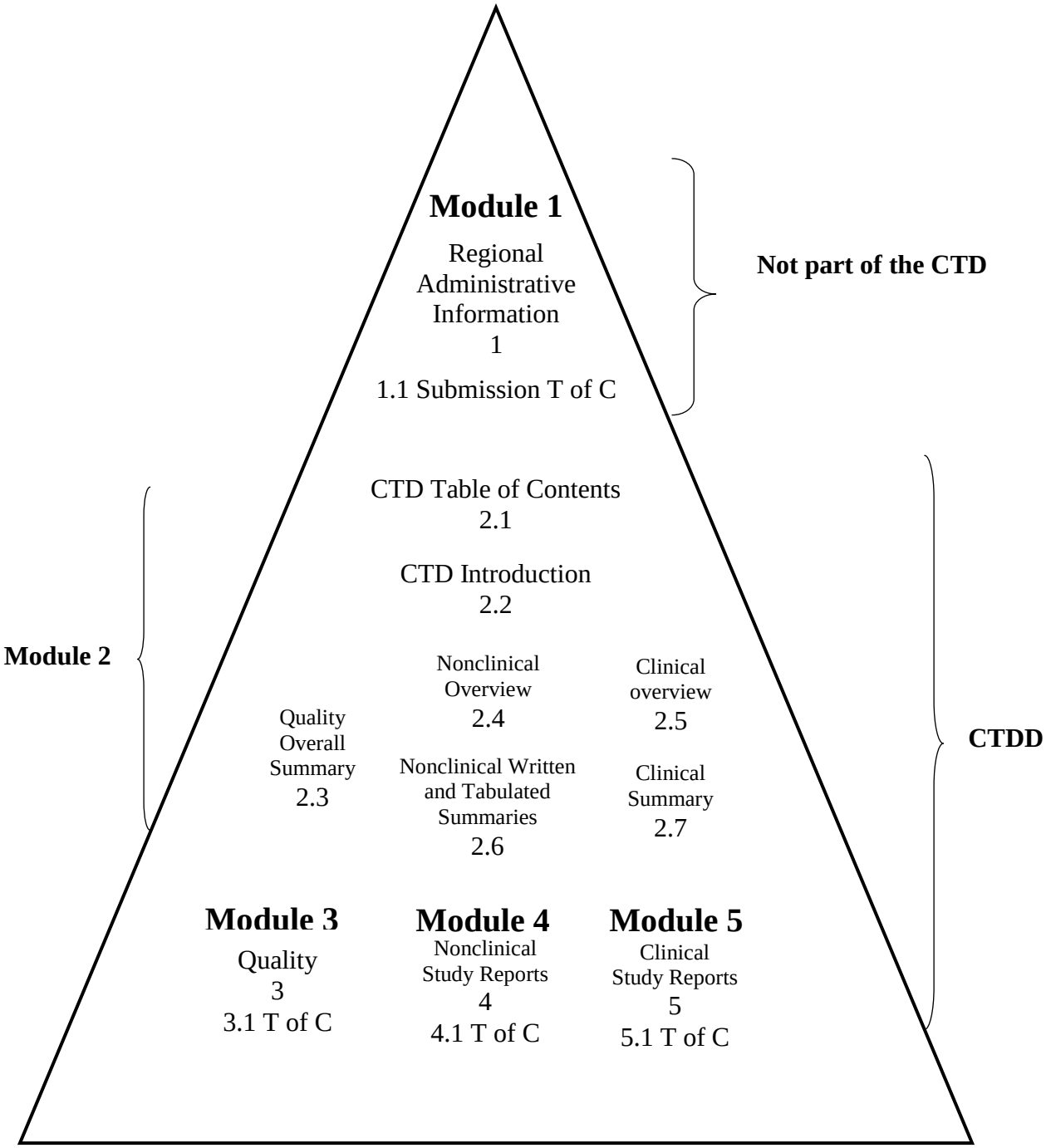
The nonclinical study reports should be presented in the order described in Appendix 1 to the Rules.

Module 5. Clinical Study Reports

The human study reports and related information should be presented in the order described in Appendix 1 to the Rules.

The overall organization of the CTD (eCTD) is presented on the following pages.

V. DIAGRAMMATIC REPRESENTATION OF THE ORGANIZATION OF THE CTD



VI. ORGANIZATION OF THE CTD FOR THE MARKETING AUTHORIZATION OF MEDICINAL PRODUCTS FOR HUMAN USE

Module 1: Administrative Information and Prescribing Information

1.1 Table of Contents of the Submission Including Module 1

1.2 Documents Specific to Each Member States (for example, application forms, prescribing information)

Module 2: CTD Summaries

2.1 CTD Table of Contents (Modules 2-5)

2.2 CTD Introduction

2.3 Quality Overall Summary

2.4 Nonclinical Overview

2.5 Clinical Overview

2.6 Nonclinical Written and Tabulated Summaries

Pharmacology

Pharmacokinetics

Toxicology

2.7 Clinical Summary

Biopharmaceutic Studies and Associated Analytical Methods

Clinical Pharmacology Studies

Clinical Efficacy

Clinical Safety

Synopses of Individual Studies

Module 3: Quality

3.1 Table of Contents of Module 3

3.2 Body of Data

3.3 Literature References

Module 4: Nonclinical Study Reports

4.1 Table of Contents of Module 4

4.2 Study Reports

4.3 Literature References

Module 5: Clinical Study Reports

5.1 Table of Contents of Module 5

5.2 Tabular Listing of All Clinical Studies

5.3 Clinical Study Reports

5.4 Literature References

VII. GRANULARITY DOCUMENT

1. Definition of a Document

A document is defined for a paper submission as a set of pages, numbered sequentially and divided from other documents by a tab (see Document Pagination and Segregation in Appendix 4 to the Rules). A document can be equated to a file for an electronic submission. The granularity of the paper and electronic submissions should be equivalent, although if a paper submission is updated to be an electronic submission, some changes in granularity could be introduced to facilitate on-going lifecycle management. In an electronic submission, a new file starts at the same point at which in a paper submission, a tab divides the documents.

In deciding whether one or more documents or files are appropriate, it should be considered that once a particular approach has been adopted, the same approach should be used throughout the life of the dossier since it is the intention that replacement documents/files be provided when information is changed.

The following tables describe the levels in the CTD/eCTD hierarchy at which documents/files should be placed and whether single or multiple documents are appropriate at each point. This describes all sections of a CTD/eCTD but for individual submissions all sections might not be applicable.

2. Module 2

Module 2	2.1		
	2.2	Introduction	
	2.3 [1]	2.3.S [2]	2.3.S.1
			2.3.S.2
			2.3.S.3
			2.3.S.4
			2.3.S.5
			2.3.S.6
			2.3.S.7
		2.3.P [3]	2.3.P.1
			2.3.P.2
			2.3.P.3
			2.3.P.4
			2.3.P.5
			2.3.P.6
			2.3.P.7
			2.3.P.8
		2.3.A	2.3.A.1
			2.3.A.2
			2.3.A.3
		2.3.R	

	2.4		
	2.5		
	2.6	2.6.1	
		2.6.2	
		2.6.3	
		2.6.4	
		2.6.5	
		2.6.6	
		2.6.7	
	2.7	2.7.1	
		2.7.2	
		2.7.3[4]	
		2.7.4	
		2.7.5	
		2.7.6	

Key

Documents rolled up to this level are not considered appropriate
The Table of Contents is only called for in the paper version of the CTD; there is no entry needed for the eCTD
One document may be submitted at this level .

1: Optionality of granularity for the Quality Overall Summary (QOS) is provided in order to accommodate different levels of complexity of products. The applicant can choose the level at which the QOS is managed.

2 : One document should be submitted for each active substance

3 : For a drug product supplied with reconstitution diluent(s), the information on the diluent(s) should be provided in a separate part "P" document

4 : One document for each indication should be submitted, although closely related indications can be within a single document

Module 3

Module 3 [1]	3.1			
	3.2	3.2.S[2]	3.2.S.1	3.2.S.1.1
				3.2.S.1.2
				3.2.S.1.3
			3.2.S.2	3.2.S.2.1
				3.2.S.2.2
				3.2.S.2.3
				3.2.S.2.4
				3.2.S.2.5

				3.2.S.2.6
			3.2.S.3	3.2.S.3.1
				3.2.S.3.2
			3.2.S.4	3.2.S.4.1
				3.2.S.4.2
				3.2.S.4.3
				3.2.S.4.4
				3.2.S.4.5
			3.2.S.5	
			3.2.S.6	
			3.2.S.7	3.2.S.7.1
				3.2.S.7.2
				3.2.S.7.3
		3.2.P[3]	3.2.P.1	
			3.2.P.2	3.2.P.2.1[4]
				3.2.P. 2.2[4]
				3.2.P.2.3
				3.2.P.2.4
				3.2.P.2.5
				3.2.P.2.6
			3.2.P.3	3.2.P.3.1
				3.2.P.3.2
				3.2.P.3.3
				3.2.P.3.4
				3.2.P.3.5
			3.2.P.4	3.2.P.4.1
				3.2.P.4.2
				3.2.P.4.3
				3.2.P.4.4
				3.2.P.4.5
				3.2.P.4.6
			3.2.P.5	3.2.P.5.1
				3.2.P.5.2
				3.2.P.5.3
				3.2.P.5.4
				3.2.P.5.5
				3.2.P.5.6

			3.2.P.6	
			3.2.P.7	
			3.2.P.8	3.2.P.8.1
				3.2.P.8.2
				3.2.P.8.3
		3.2.A	3.2.A.1	
			3.2.A.2	
			3.2.A.3	
		3.2.R		
	3.3	One file per reference Note 6		

Key

Documents rolled up to this level are not considered appropriate
The Table of Contents is only called for in the paper version of the CTD; there is no entry needed for the eCTD
One or multiple documents can be submitted at this level .

1 : In choosing the level of granularity for this Module, the applicant should consider that, when relevant information is changed at any point in the product's lifecycle, replacements of complete documents/files should be provided in the CTD and eCTD.

2 : For a drug product containing more than one drug substance, the information requested for part "S" should be provided in its entirety for each drug substance.

3 : For a drug product supplied with reconstitution diluent(s), the information on the diluent(s) should be provided in a separate part "P", as appropriate.

4 : The lower level of headings included in CTD Quality part at this point are unlikely to be individual documents or files.

6 : Literature References should be listed in the tables of contents.

Module 4

Module 4	4.1				
	4.2	4.2.1	4.2.1.1	Studies[1]	
			4.2.1.2	Studies[1]	
			4.2.1.3	Studies[1]	
			4.2.1.4	Studies[1]	
		4.2.2	4.2.2.1	Studies[1]	
			4.2.2.2	Studies[1]	
			4.2.2.3	Studies[1]	
			4.2.2.4	Studies[1]	
			4.2.2.5	Studies[1]	
			4.2.2.6	Studies[1]	

			4.2.2.7	Studies[1]	
		4.2.3	4.2.3.1	Studies[1]	
			4.2.3.2	Studies[1]	
			4.2.3.3	4.2.3.3.1	Studies[1]
				4.2.3.3.2	Studies[1]
			4.2.3.4	4.2.3.4.1	Studies[1]
				4.2.3.4.2	Studies[1]
				4.2.3.4.3	Studies[1]
			4.2.3.5	4.2.3.5.1	Studies[1]
				4.2.3.5.2	Studies[1]
				4.2.3.5.3	Studies[1]
				4.2.3.5.4	Studies[1]
			4.2.3.6	Studies[1]	
			4.2.3.7	4.2.3.7.1	Studies[1]
				4.2.3.7.2	Studies[1]
				4.2.3.7.3	Studies[1]
				4.2.3.7.4	Studies[1]
				4.2.3.7.5	Studies[1]
				4.2.3.7.6	Studies[1]
				4.2.3.7.7	Studies[1]
	4.3	One file per reference[2]			

Key

Documents rolled up to this level are not considered appropriate
The Table of Contents is only called for in the paper version of the CTD; there is no entry needed for the eCTD
One or multiple documents may be submitted at this level .

1 : Typically, a single document should be provided for each study report included in Module 4. However, where the study report is large, (e.g., a carcinogenicity study), the applicant can choose to submit the report as more than one document. In this case, the text portion of the report should be one document and the appendices can be one or more documents. In choosing the level of granularity for these reports, the applicant should consider that, when relevant information is changed at any point in the product's lifecycle, replacements of complete documents/files should be provided.

2 : Literature References should be listed in the tables of contents.

Module 5

Module 5	5.1			
	5.2			
	5.3	5.3.1	5.3.1.1	Studies[1]
			5.3.1.2	Studies[1]

			5.3.1.3	Studies[1]
			5.3.1.4	Studies[1]
		5.3.2	5.3.2.1	Studies[1]
			5.3.2.2	Studies[1]
			5.3.2.3	Studies[1]
		5.3.3	5.3.3.1	Studies[1]
			5.3.3.2	Studies[1]
			5.3.3.3	Studies[1]
			5.3.3.4	Studies[1]
			5.3.3.5	Studies[1]
		5.3.4	5.3.4.1	Studies[1]
			5.3.4.2	Studies[1]
		5.3.5 Note 2	5.3.5.1	Studies[1]
			5.3.5.2	Studies[1]
			5.3.5.3	Studies[1]
			5.3.5.4	Studies[1]
		5.3.6		
		5.3.7	Studies[1]	
	5.4	One file per reference[3]		

Key

Documents rolled up to this level are not considered appropriate
The Table of Contents is only called for in the paper version of the CTD; there is no entry needed for the eCTD
One document can be submitted at this level
One document or multiple documents may be submitted at this level .

1: The applicants should ordinarily provide the study reports as multiple documents (a synopsis, a main body of the study report and appropriate appendices). Appendices should be organized in accordance with Appendix 1 to the Rules of the Good Clinical Practice of the Eurasian Economic Union, which describes the content and format of the clinical study report. In choosing the level of granularity for reports the applicant should consider that, when relevant information is changed at any point in the product's lifecycle, replacements of complete documents/files should be provided.

2 : For applications in support of more than one indication, this section should be repeated for each indication.

3 : Literature References should be listed in the tables of content.

VIII. DOCUMENT PAGINATION AND SEGREGATION

1. General requirements

Every document should be numbered starting at page one, except for individual literature references, where the existing journal page numbering is considered sufficient. Applicants need not display the number as '1 of n' where n is the total number of pages in the document.

Additionally, all pages of a document should include a unique header or footer that briefly

identifies its subject matter. In a paper-based drug submission, a similar identifier should be used on a tab that precedes the document, to facilitate finding that document within the dossier. An abbreviation of the full section number and title can be used.

If a section contains more than one document, a specific Table of Contents for that section can be included to identify the chronology and titles of the documents contained therein, e.g.

• Tab with "3.2.S.4.2 Analytical Procedures"

    o Table of Contents, listing the title of Procedure A, Procedure B, Procedure C

• Tab with "3.2.S.4.2 "Procedure A";

    o Procedure A (i.e. document, page 1-n)

• Tab with "3.2.S.4.2 "Procedure B";

    o Procedure B (i.e. document, page 1-n)

• Tab with "3.2.S.4.2 "Procedure C";

    o Procedure C (i.e. document, page 1-n)

If a section contains only a single document (e.g. 3.2.S.1.1 Nomenclature), only a tab identified by "3.2.S.1.1 Nomenclature" should precede the document.

2. Section Numbering within Documents

In order to avoid 5th, 6th etc. level subheading numbering (e.g. 2.6.6.3.2.1) within a document, the applicant can use a shortened numbering string. In this case, the document number and the name (e.g. 2.6.6 Toxicology Written Summary) should appear in page headers or footers and then section numbering within the document can be used, for example, 1, 1.1, 2, 3, 3.1, 3.2 etc. Use of the full numbering string (e.g. 2.6.6.3.2.1) is also considered acceptable.

3. Table of Contents Formatting

3.1. Module 2

The 2.1 CTD Table of Contents should go down to the third (e.g. 2.3.S) or fourth (e.g. 2.3.S.1) level, depending on how a document is defined for the Quality Overall Summary. (See Definition of a document for Module 2.)

3.2. Module 3

The Table of Contents provided under 3.1 should cover the high-level section numbering, the associated section heading and the Volume number in the order that they appear in the drug submission. This Table of Contents would be used to identify the contents of Module 3 as defined in Appendix 1 to the Rules. It should go down to the fifth level only (e.g. 3.2.P.2.1). Note that additional subsections and subheadings are defined in Appendix 1 to the Rules beyond this level (e.g. under 3.2.P.2) and this formatting should be used within the dossier, despite not being included in the 3.1 Table of Contents. The lower level Table of Contents described under Document Pagination and Segregation should be excluded from the 3.1 Table of Contents.

At the applicant's discretion, if there is a desire to introduce additional headers or subsection numbering beyond those which are defined in the Appendix 1 to the Rules, these should only be included within a document and should be created neither as a separate document nor as a new subsection. In this case, a specific Table of Contents for that document can be included to identify

the chronology and titles of the subsections contained therein. These documents and subsections should not appear in the 3.1 Table of Contents.

Furthermore, additional attachments or appendices should not be incorporated into this formatting, except as a document under a section where multiple documents might be provided. In this case, a cross-reference should be made within the relevant section to the attached or appended document. If there is a desire to append or attach additional information to a section that is comprised of only one document, this information should be incorporated within that document.

All Table of Contents title entries should either correspond to heading names and section numbering as defined in Appendix 1 to the Rules or to identifiers appearing on tabs (for a paper-based drug submission only), preferably by their full title, which should easily identify any abbreviated title that might be used on the corresponding tab. The Table of Contents should not specify any page numbers.

Literature References should be listed in a Table of Contents specific for this section.

3.3. Module 4

The Table of Contents for Module 4 should include all of the numerical items listed in Appendix 1 to the Rules in order to identify all of the important components of the application (for example, 4.2.3.5.1 Fertility and early embryonic development) and should continue down to at least the level of the study report. Thus each study report should be identified in the table of contents. The sections of a study report could be identified in the Module 4 Table of Contents of the dossier or only in the Table of Contents of the individual study report.

Illustration of part of the Module 4 Table of Contents

4.2.3.2 Repeat-Dose Toxicity

Study aa-aaa: 30 day repeat dose toxicity study with Drug C in rat

Study bb-bbb: 6 month repeat dose toxicity study with Drug C in rat

Study cc-ccc: 30 day repeat dose toxicity study with Drug C in dog

Study dd-ddd: 6 month repeat dose toxicity study with Drug C in dog

4*.2.3.3 Genotoxicity*

4.2.3.3.1 In vitro

Study ee-eee: Ames test with Drug C etc.

Module 5

The Table of Contents for Module 5 should include all of the numerical items listed in the Appendix 1 to the Rules in order to identify all of the important components of the application (for example, 5.3.5.1.1 Placebo Controlled Trials) and should continue down to at least the level of the clinical study report. Thus each clinical study report should be identified in the table of contents. The sections of a clinical study report (see Appendix 1 to the Rules of the Good Clinical Practice of the Eurasian Economic Union) could be identified in the Module 5 Table of Contents of the dossier or only in the Table of Contents of the individual clinical study report.

Illustration of part of the Module 5 Table of Contents

5.3.5 Indication Z - Reports of Efficacy and Safety Studies

5.3.5.1 Indication Z - Study Reports of Controlled Clinical Trials Pertinent to the Claimed Indication

5.3.5.1.1 Indication Z - Placebo Controlled Trials

Study xx-xxx: A double blind, placebo-controlled trial of Drug A in Indication Z

Study yy-yyy: A double blind……

5.3.5.1.2 Indication Z - Active Controlled Trials

Study zz-zzz: A double blind, active controlled trial of Drug A vs. Drug C in Indication Z

5.3.5 Indication Q - Reports of Efficacy and Safety Studies

5.3.5.1 Indication Q - Study Reports of Controlled Clinical Trials Pertinent to the Claimed Indication etc.

APPENDIX 6
to the Rules of authorization and
assessment of medicinal products
for human use

NON-CLINICAL TEMPLATE

(template)

CRITICAL ASSESSMENT REPORT
Non-Clinical Aspects

_____

(name of the medicinal product, dosage form, strengths)

Assessor:	
Start of the procedure:	
Date of this report:	
Deadline for comments:	

ADMINISTRATIVE INFORMATION

Application number:	
Brand name of the medicinal product:	
International Non-proprietary Name (INN) or common name of active substance(s):	
Applicant:	
Applied indications:	
Pharmaco-therapeutic group (ATC code):	
Dosage form and strength(s):	
Names of the Rapporteur assessors (internal and external):	Quality: Name: Tel (fax): Email: Non-clinical: Name: Tel (fax): Email: Clinical: Name: Tel (fax): Email:

List of abbreviations

NON-CLINICAL CRITICAL ASSESSMENT

1. Introduction

1.1.Type of application and aspects on development

1.2.Good Laboratory Practice aspects

2. Pharmacology (Modules 2.6.2 and 4.2.1)

Brief summary

Assessor's comment

Physical chemistry:
Structure of the active substance
(insert the figure)
Site of labelling (see structure).
Isomerism.
Molecular weight.
Solubility in water.
Pka.
Distribution coefficient.
Solubility in other solvents.
Stability.
Possible chirality and its consequences.

Assessor's comment

2.1. Primary pharmacodynamics

Assessor's comment

2.2. Secondary pharmacodynamics

Assessor's comment

2.3. Safety pharmacology

Assessor's comment

2.4. Pharmacodynamic drug interactions

Assessor's comment

2.5. Assessor's overall conclusions on pharmacology

Assessor's comment

3. Pharmacokinetics (Modules 2.6.4 and 4.2.2)

Pharmacokinetic studies

Assessor's comment

3.1. Methods of analysis

Assessor's comment

3.2. Absorption

Examples of tables to tabulate absorption data:

Study ID	Species	N	Dose (mg/kg)	Route of administration	Analysis	C_{max}	t_{max}	AUC
A								
B								

Study ID	Species	N	Dose (mg/kg)	Route of administration	Analysis	t½, el	V_d	Cl_t	F (%)
A									
B									

Re a)
b)

Assessor's comment

3.3. Distribution

Assessor's comment

3.4. Metabolism

Assessor's comment

3.5. Excretion

Species	N	Dose (mg/kg)	Route	Analysis	Urine (% dose)	Faeces (% dose)	Bile (% dose)	Recovery (% dose)	Time (h)
					±	±	±	±	±
					±	±	±	±	±

Assessor's comment

3.6. Pharmacokinetic drug interactions

Assessor's comment

3.7. Other pharmacokinetic studies

Assessor's comment

3.8. Assessor's overall conclusions on pharmacokinetics

4. Toxicology (Modules 2.6.6 and 4.3.3)

4.1. Single dose toxicity

Example of a table for single dose toxicity studies:

Study ID	Species /sex/ number/ group	Dose/route	Approx. lethal dose / observed max non-lethal dose	Major findings

Assessor's comment

4.2. Repeated-dose toxicity

Example of a table to show repeat-dose toxicity studies:

Study ID	Species/sex/ number/group	Dose/route	Duration	NOEL/NOAEL (mg/kg/day)	Major findings

Assessor's comment

Toxicokinetics

Example of a table to show toxicokinetic studies:

Study ID	Daily dose (xx/xx)	Animal AUC (ng×h/ml)*	Animal : Humans XXX Exposure Multiple
		♂ ♀	♂ ♀

Note: *For comparison, it is desirable to use the AUC values for the non-bound fraction of the compound.

Assessor's comment

Interspecies comparison

Example of a table to compare the exposure in the animal studies with the clinical exposure:

Study ID	Daily dose (xx/xx)	Animal AUC (ng×h/ml)*		Cmax		$t_{1/2}$	
		♂	♀	♂	♀	♂	♀

Assessor's comment

4.3. Genotoxicity

Example table of the overview of genotoxicity studies:

Type of test/study ID/GLP compliance	Test system	Concentrations/ concentration range/metabolising system	Results: positive/negative/equivocal
Gene mutations in bacteria	Salmonella strains	+/- S9	
Gene mutations in mammalian cells	Chinese hamster ovary cells (CHO cells),	+/- S9	

	HGPRT-locus, human lymphocytes	
Chromosomal aberrations in vivo	Mouse, micronuclei in bone marrow	+/- S9

Assessor's comment

4.4. Carcinogenicity

4.4.1. Long-term studies

Example table of the overview of carcinogenicity studies performed:

Study ID /GLP compliance	Dose/route	Exposure (AUC)	Species/no. of animals	Major findings

Example table of tumor findings in "Study XX":

Tumour findings	Control	Low dose	Mid dose	High dose
	Male Female			

Assessor's comment

4.4.2. Short or medium-term studies

Assessor's comment

4.4.3. Other studies

Assessor's comment

4.5. Reproductive and developmental toxicity

Example summary table of the performed studies:

Study type/ Study ID / GLP compliance	Species; number Female / group	Route & dose	Dosing period	Major findings	NOAEL (mg/kg & AUC)
Male fertility					
Female fertility					
Embryo-foetal development					F_0 F_1
Prenatal and postnatal development					

Assessor's comment

4.5.1. Fertility and early embryonic development

Assessor's comment

4.5.2. Embryo-foetal development

Assessor's comment

4.5.3. Prenatal and postnatal development, including maternal function

Assessor's comment

4.5.4. Studies in which juvenile animals are dosed and/or further evaluated

Assessor's comment Conclusion on reproductive toxicity

4.6. Local tolerance

Assessor's comment

4.7. Other toxicity studies

Assessor's comment

4.7.1. Antigenicity

Assessor's comment

4.7.2. Immunotoxicity

Assessor's comment

4.7.3. Dependence

Assessor's comment

4.7.4. Metabolites

Assessor's comment

4.7.5. Studies on impurities

Assessor's comment

4.7.6. Other studies

Assessor's comment

4.8. Assessor's overall conclusions on toxicology

5. List of references

6. List of questions proposed by the assessor

MAJOR OBJECTIONS

Pharmacology

Pharmacokinetics

Toxicology

OTHER CONCERNS

Pharmacology

Pharmacokinetics

Toxicology

RECOMMENDATIONS

7. Recommended conditions for marketing authorization and summary of product characteristics, package leaflet (patient leaflet) and package design.

APPENDIX 7
to the Rules of authorization and assessment of medicinal products for human use

CLINICAL TEMPLATE

(template)

CRITICAL ASSESSMENT REPORT
Clinical Aspects

ADMINISTRATIVE INFORMATION

Brand name of the medicinal product:	
International Non-proprietary Name (INN) or common name of active substance(s):	
Applicant:	
Applied Indications:	
Pharmaco-therapeutic group (ATC code):	
Pharmaceutical form and strength(s):	
Assessor's contact person:	Name: Tel (fax): Email:
Assessors' details (internal and external):	Quality: Name: Tel (fax): Email: Non-clinical: Name: Tel (fax): Email: Clinical: Name: Tel (fax): Email:
Assessors' details (internal and external):	Quality: Name: Tel (fax): Email: Non-clinical: Name: Tel (fax): Email: Clinical: Name: Tel (fax): Email:

List of abbreviations:

CLINICAL CRITICAL ASSESSMENT

1. Introduction

1.1. Type of application and aspects on development:

- Legal basis;
- Approval under exceptional circumstances;
- Biosimilar application;
- Compliance with the guidelines on medicinal product development / scientific advice;
- Significance of paediatric studies.

1.2. Good Clinical Practice (GCP) compliance

1.3. Orphan medicinal products

According to the conclusion of the competent authorities (Opinion dated 00/00/00) the prevalence of the "condition" <state the condition> is <XX> per 10 000 individuals within the Eurasian Economic Union Member States / N/A.

2. Clinical pharmacology

2.1. Pharmacokinetics

2.1.1 Introduction

2.1.2 Methods

Analytical methods and procedures

Assessor's comment

Pharmacokinetic data analysis

Assessor's comment

Statistical analysis

Assessor's comment

2.1.3. Absorption

Bioavailability

Assessor's comment

Bioequivalence

Assessor's comment

Influence of food

Assessor's comment

2.1.4. Distribution

Assessor's comment

2.1.5. Elimination

Excretion

Assessor's comment

Metabolism

Assessor's comment

Inter-conversion

Assessor's comment

Pharmacokinetics of metabolites

Assessor's comment

Consequences of possible genetic polymorphism

Assessor's comment

2.1.6. Dose proportionality and time dependency

Dose proportionality

Assessor's comment

Time dependency

Assessor's comment

2.1.7. Intra- and inter-individual variability

Assessor's comment

2.1.8. Pharmacokinetics in target population

Assessor's comment

2.1.9. Special populations

Impaired renal function

Assessor's comment

Impaired hepatic function

Assessor's comment

Gender

Assessor's comment

Race

Assessor's comment

Weight

Assessor’s comment

Elderly

	Age 65–74 (Older subjects number /total number)	Age 75–84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
PK Trials			
Assessor’s comment			

Children

Assessor’s comment

Assessor's overall comments on pharmacokinetics in special populations

2.1.10. Interactions

In vitro

Assessor’s comment

In vivo

Assessor’s comment

Assessor's overall comments on Interactions

2.1.11. Exposure relevant for safety evaluation

Assessor’s comment

2.1.12. Assessor’s overall conclusions on pharmacokinetics

2.2. Pharmacodynamics

2.2.1 Introduction

2.2.2 Mechanism of action

Assessor’s comment

2.2.3. Primary pharmacology

Assessor’s comment

2.2.4. Secondary pharmacology

Assessor's comment

2.2.5. Relationship between plasma concentration and effect

Assessor's comment

2.2.6. Pharmacodynamic interactions with other medicinal products or substances

Assessor's comment

2.2.7. Genetic differences in the pharmacodynamic response

Assessor's comment

2.2.8. Assessor's overall conclusion on pharmacodynamics

_____
_____
_____

3. Clinical efficacy

3.1. Introduction

Example table for study details:

Study ID	No. of study centers /loca-tions	Design	Study posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis, inclusion criteria	Primary endpoints

3.2. Dose response studies and main clinical trials

Assessor's comment

3.3. Dose response study(ies)

Assessor's comment

3.4. Main study(ies)

Assessor's comment

Methods

Study participants

Assessor's comment

Treatments

Assessor's comment

Objectives

Assessor's comment

Outcomes/endpoints

Assessor's comment

Sample size

Assessor's comment

Randomization

Assessor's comment

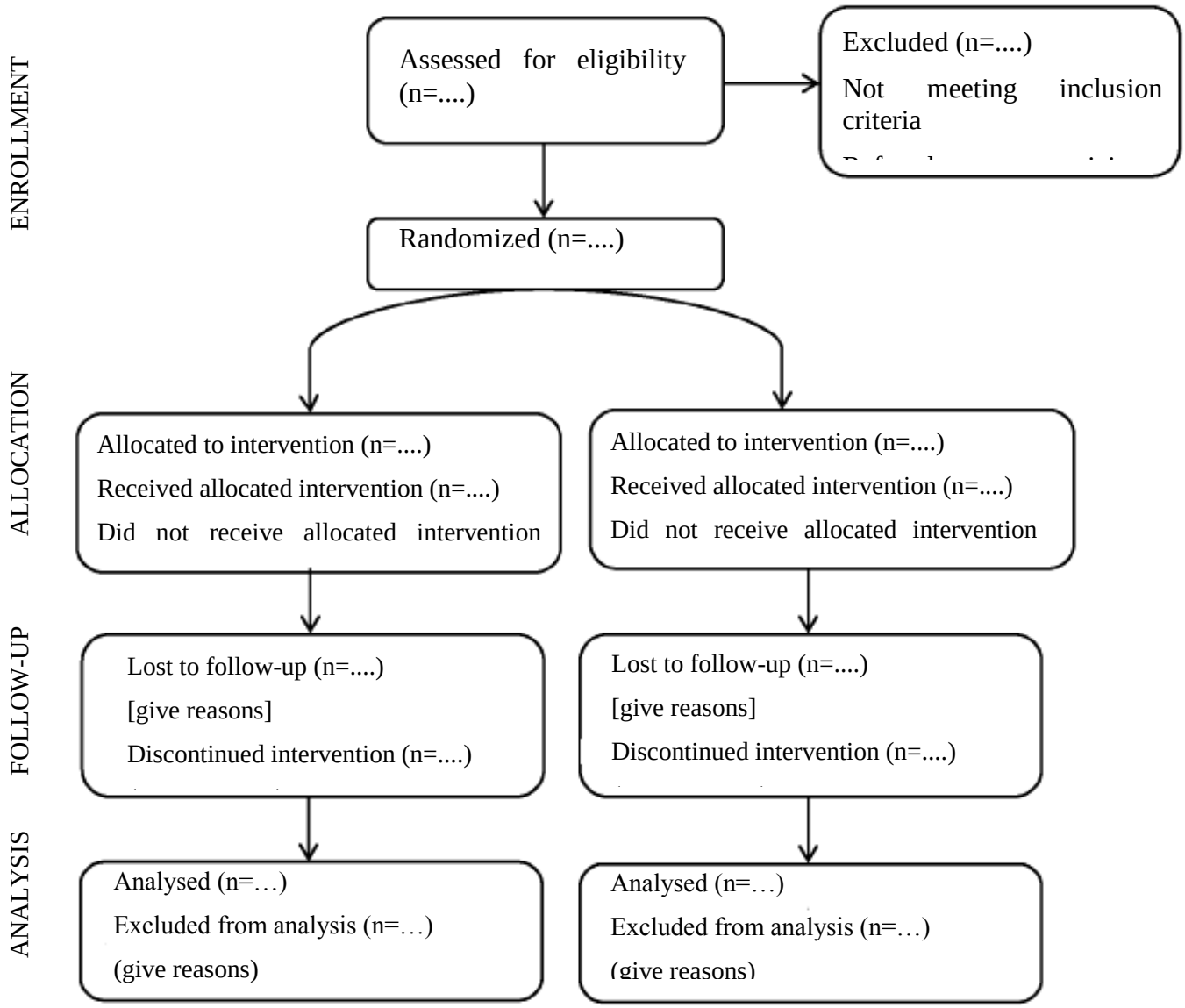
Blinding (masking)

Assessor's comment

STATISTICAL METHODS

Results

Participant flow (to be used and amended as appropriate)



Recruitment

Assessor's comment

Conduct of the study

Assessor's comment

Baseline data

Assessor's comment

Numbers analysed

Assessor's comment

Outcomes and estimation

Assessor's comment

Ancillary analyses

Assessor's comment

Summary of main efficacy results

The following tables summarize the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Summary of efficacy for trial <trial>

Title (as indicated in the study report)			
Study identifier	code list all codes starting with the protocol number followed by – as available - EudraCT number, ISRCT number, other codes that allow cross-referencing to publications		
Study design	free text describe key elements of the design (cross-over, parallel, factorial, dose-escalation, fixed-dose response) including randomization, blinding, allocation concealment, mono-/multi-center, etc.		
	duration of the main phase: duration of the run-in phase: duration of the extension phase:		time time not applicable time not applicable
Hypothesis	superiority equivalence non-inferiority exploratory: specify		
Treatment groups (add as many rows as needed to describe the treatment groups)	group descriptor (provide abbreviation for use later in the table of the results section)		treatment duration number of randomized subjects
	group descriptor		treatment duration number of randomized subjects
	group descriptor		treatment duration number of randomized subjects
Clinical study endpoints (add as many rows as needed to describe the endpoints; for the secondary endpoints select the ones considered most relevant and reported in the results section)	Co-primary endpoint	label (generate abbreviation for later use in the table of the results section)	free text (provide a brief description)
	Secondary other: specify endpoint	label	free text (provide brief description)
	Secondary other:	label	free text (provide brief description)

	specify endpoint			
Database lock	date			
Results and analysis (present the result separate for each analysis that is considered relevant for the conclusion on the trial; in any case the pre-specified primary analysis should be presented)				
Analysis description	primary analysis			
Analysis population and time point description	Intent to treat Per protocol other: specify (consider adding a brief description of the definition of the population) time point			
Descriptive statistics and estimated variability	treatment group	group descriptor (as per above terminology)	group descriptor (as per above terminology)	group descriptor (as per above terminology)
	number of subjects	n	n	n
	endpoint (label as above) statistic (e.g. mean, median, etc.)	point estimate	point estimate	point estimate
	variability statistic (e.g. standard deviation, confidence interval, etc.)	variability	variability	variability
	study endpoint (statistic)	point estimate	point estimate	point estimate
	variability statistic	variability	variability	variability
	endpoint statistic	point estimate	point estimate	point estimate
	variability statistic	variability	variability	variability
Effect estimate per comparison (add as many rows as needed to describe the relevant statistical testing performed)	co-primary endpoint	comparison groups	group descriptors (as per above terminology)	
		test statistic (e.g. difference between groups)	point estimate	
		variability statistic (e.g. confidence interval, etc.)	variability	
		P-value (indicate statistical test used, e.g. ANOVA)	P-value	
	co-primary secondary	comparison groups	group descriptor	
		test statistic	point estimate	

	other: specify endpoint (indicate the endpoint using the terminology in the *Endpoints and definitions* section)	variability statistic	variability
		P-value	P-value
	co-primary secondary other: specify endpoint	comparison groups	group descriptor
		test statistic	point estimate
		variability statistic	variability
		P-value	P-value
Notes	free text (consider amongst others the following information: reasons for drop-outs critical findings with regard to the analysis)		
Analysis description	Secondary analysis Co-primary Analysis Other: specify (also indicate if the conduct of the analysis was pre-specified)		
repeat all the above sections for each analysis that is considered relevant			

3.5. Clinical trials in special populations

	Age 65–74 (Older subjects number /total number)	Age 75–84 (Older subjects number /total number)	Age 85+ (Older subjects number /total number)
Controlled trials			
Non controlled trials			

Assessor's comment

3.6. Analysis performed across trials (pooled analyses and meta-analysis)

Assessor's comment

3.7. Supportive study(ies)

Assessor's comment

3.8. Assessor's overall conclusions on clinical efficacy

Conclusions on clinical efficacy

Design and conduct of clinical studies
Efficacy data and additional analyses
Conclusions on clinical efficacy

4. Clinical safety

4.1. Introduction

Assessor's comment

4.2. Subject exposure

Example of a table: Patient exposure (cut off)

	Subjects enrolled	Subjects exposed	Subjects exposed to the proposed dose range	Subjects with long term* safety data
Placebo-controlled studies				
Active-controlled studies				
Open studies				
Post-marketing studies				
Compassionate use				

*This refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

Assessor's comment

4.3. Adverse events

Assessor's comment

4.4. Serious adverse events and deaths

Assessor's comment

4.5. Laboratory findings

Assessor's comment

4.6. Safety in special populations

MedDRA terms Total adverse events Serious adverse events (total)	age < 65 number (percentage)	age 65–74 number (percentage)	age 75–84 number (percentage)	age 85+ number (percentage)
fatal				
hospitalization / prolonged existing hospitalization				
life-threatening				

disability / incapacity				
other (medically significant) adverse event leading to drop-out				
Psychiatric disorders Nervous system disorders				
Accidents and injuries Cardiac disorders Vascular disorders Cerebrovascular disorders				
Infections and infestations Anticholinergic syndrome Quality of life decreased Sum of postural hypotension, falls, black outs, syncope, dizziness, ataxia, fractures				
Other AEs appearing more frequently in older subjects				

Assessor's comment

4.7. Immunological events

Assessor's comment

4.8. Safety related to drug-drug interactions and other interactions

Assessor's comment

4.9. Discontinuation due to adverse events

Assessor's comment

4.10. Post marketing experience

Assessor's comment

4.11. Assessor's overall conclusions on clinical safety

Conclusions on clinical efficacy
Conclusions on clinical safety

5. Pharmacovigilance

5.1. Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Union or in a third country has been provided.

The assessors consider that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Eurasian Economic Union or in a third country.

The assessor considers that the Pharmacovigilance system as described by the applicant has the following deficiencies:<list the deficiencies>.

Provided that the deficiencies are rectified prior to the applicant placing the medicinal product on the market, the assessment organization may consider that the Pharmacovigilance system will fulfil the requirements. The applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.

Assessor's comment

5.2. Risk Management Plan

Issues and/or concerns for consideration by the pharmacovigilance assessor when assessing the RMP

_____

_____

6. List of references:

_____

_____

_____

_____

7. List of questions as proposed by the assessor

Clinical aspects:

a) Major objections:

Pharmacokinetics

Pharmacodynamics

Efficacy

Safety

Pharmacovigilance system

Risk management plan

b) Other concerns:

Pharmacokinetics

Pharmacodynamics

Efficacy

Safety

Pharmacovigilance system

Risk management plan

c) Recommendations:

_____

_____

8. Recommended conditions for marketing authorization and approval of the summary of product characteristics

User Consultation:

_____
_____
_____

APPENDIX 8
to the Rules of authorization
and assessment of medicinal products
for human use

QUALITY TEMPLATE

Completion guide: preset text templates are bracketed in this document using < > and in italics; text template fragments to be filled by entering specific versions of the text on the specified property (parameter) are bracketed in curly brackets using {} with indication of the property (parameter) to be added in italics; , explanations are given in italics in square brackets [ ].

(template)

CRITICAL ASSESSMENT REPORT
Quality Aspects
of a medicinal product

_____

(name of the medicinal product, pharmaceutical form, strengths)

Assessor:	
Start of the procedure:	
Date of this report:	
Deadline for comments:	

LIST OF ABBREVIATIONS

_____

_____

I. QUALITY CRITICAL ASSESSMENT

1. Request for manufacturing site inspection prior to authorization

---

2. Introduction

Name:	
Dosage dosage form and strength:	
Procedure:	
Therapeutic class or indication:	
Proposed dosage range:	

3. Active substance

(API, Module 3.2.S)

Notes:

1. It should be mentioned whether a Certificate of Suitability to the Monographs of the European Pharmacopoeia (CEP) or Active Substance Master File (ASMF) procedure or full information in the dossier of the API in the dossier is used.
2. If the Active Substance Master File (ASMF) is used, it should be mentioned that an assessment of the ASMF is provided in a separate ASMF Assessment Report with a confidential Annex on the restricted part.
3. Where there is more than one ASMF cited in the dossier, a separate report is provided for each ASMF.
4. Letters of Access in relation to specific drug products should be described for the product in question.
5. When a CEP or ASMF is used, only Section 3.4 *Control of Active Substance* and 3.5 *Reference Standards or Materials* relating to the product manufacturer need completing, unless the applicant has provided additional data e.g. 3.2.S.7 stability data to support a longer re-test period.
6. The questions to the restricted part of the ASMF reports will not be sent to the MAH but only to the relevant ASM/holder of the ASMF.
7. Where ASMF or CEP is applicable, clarify the source (applicant or ASMF holder or CEP holder) and level of details to be drafted in the assessment report.
8. The assessment of the drug substance in this AR should only address additional information provided by the applicant, which is not included in the open part as provided by the ASMF holder. In case a full dossier for the Active Substance is provided by the applicant the full assessment of the active substance should be included in the report.

3.1. General information on starting and raw materials (Module 3.2.S.1)

API name (Module S.1.1)

International non-proprietary name (INN):	
Chemical name:	
Other name (where applicable):	
Name on the IUPAC nomenclature:	
CAS registry number:	
Laboratory code:	

Molecular formula:	
Relative molecular mass:	

Structural formula of API (Module S.1.2)

General properties of API (Module S.1.3)

Physical characteristics:	
Solubility:	
pKa-value:	
Solution pH (where possible)	
Melting point (for solids)	
Partition coefficient:	
Hygroscopicity:	
Stereochemistry:	
Polymorphism:	
Degree of crystallinity (for solids)	

Assessor's comment

3.2. Manufacture of API (Module 3.2.S.2)

3.2.1. Manufacturers (Section S.2.1)

3.2.2. Compliance with the Good Manufacturing Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission (hereinafter referred to as Commission) (GMP)

3.2.3. Description of manufacturing process and process controls (Section S.2.2)

3.2.4. Control of of materials (Section S.2.3)

3.2.5. Control of critical steps and intermediates (Section S.2.4)

3.2.6. Process validation and/or evaluation (Section S.2.5)

3.2.7. Manufacturing process development (Section S.2.6)

Assessor's comment

3.3. Characterization of API (Module 3.2.S.3)

3.3.1. Elucidation of structure and other characteristics (Section S.3.1).

3.3.2. Impurities (Section S.3.2)

Assessor's comment

3.4. Control of active substance (Module 3.2.S.4)

3.4.1. Specifications (Section S.4.1)

Table S.4-1

Specification

Specification parameter	Test method	Test limits

3.4.2. Analytical procedures (Section S.4.2)

3.4.3. Validation of analytical procedures (Section S.4.3)

Table S.4-2

Summary of validation of analytical procedures

	Analytical procedure			
Accuracy				
Reproducibility: repeatability intermediate precision (where available)				
Specificity				
Detection limit				
Quantitation limit				
Linearity				
Range				
Robustness				
Solution stability				

Note: + indicates that the parameter is acceptably tested, – indicates that the parameter is not tested, ? indicates that questions remains before the parameter is judged to be acceptable.

3.4.4. Batch analyses (Section S.4.4)

3.4.5. Justification of specification (Section S.4.5)

Assessor's comment

3.5. Reference Standards or Materials (Module 3.2.S.5)

Assessor's comment

3.6. Container closure system (Module 3.2.S.6)

Assessor's comment

3.7. Stability (Module 3.2.S.7)

3.7.1. Stability summary and conclusion (Section: S.7.1)

Table S. 7-1

Stability studies

Temperature, °C; Relative humidity (RH), %	*n* batches *x* months	Batch size	Package
25 °C / RH 60%		Production scale / Pilot scale	Intended for marketing
40 °C / RH 75%			

3.7.2. Post-approval stability protocol and stability commitments (Section S.7.2)

3.7.3. Stability data (Section S.7.3)

The stability data on which the summary and conclusion in S.7.1 is based, is included in the dossier.

Assessor's comment

4. Finished medicinal product (Module 3.2.P)

4.1. Description and composition of the finished medicinal product (Module 3.2.P.1)

The composition of <medicinal product> is presented in Table P.1-1 below.

Table P. 1-1

Complete composition of <medicinal product>

Ingredient	Reference	<Name> Amount (<name>)	<Name> Amount (<name>)	Function
				active

Note: When approving a line extension, the number of '<Name> Amount (<name>)' columns shall correspond to the number of strengths applied for authorization.

Assessor's comment

4.2. Pharmaceutical development (Module 3.2. P.2)

4.2.1. Components of the finished medicinal product (Section P.2.1)

4.2.2. Active substance (Section P.2.1.1)

4.2.3. Excipients (Section P.2.1.2)

4.2.4. Finished medicinal product (Section P.2.2)

4.2.5. Formulation development (Section P.2.2.1)

Bioequivalence study and reference product / Clinical formulation

4.2.6. Overages (Section P.2.2.2)

4.2.7. Physicochemical and biological properties (Section P.2.2.3)

4.2.8. Manufacturing process development (Section P.2.3)

4.2.9. Container closure system (Section P.2.4)

4.2.10. Microbiological attributes (Section P.2.5)

4.2.11. Compatibility (Section P.2.6)

Assessor's comment

4.3. Manufacturing process (Module 3.2.P.3)

4.3.1. Manufacturers (Section P.3.1)

4.3.2. Batch formula (Section P.3.2)

4.3.3. Description of manufacturing process and process controls (Section P.3.3)

4.3.4. Controls of critical steps and intermediates (Section P.3.4)

4.3.5. Process validation and/or evaluation (Section P.3.5)

Assessor's comment

4.4. Control of excipients (Module 3.2.P.4)

4.4.1. Specifications (Section P.4.1)

4.4.2. Analytical procedures (Section P.4.2)

4.4.3. Validation of analytical procedures (Section P.4.3)

4.4.4. Justifications of specifications (Section P.4.4)

4.4.5. Excipients of human and animal origin (Section P.4.5)

4.4.6. Novel excipients (Section P.4.6)

Assessor's comment

4.5. Control of finished medicinal product (Module 3.2.P.5)

4.5.1. Specifications (Section P.5.1)

Table P. 5-1

Release and shelf-life specifications

Specification parameter	Test method	Test limits

4.5.2. Analytical procedures (Section P.5.2)

4.5.3. Validation of analytical procedures (Section P.5.3)

Table P. 5-2

Summary of validation of analytical procedures

	Analytical procedure			
Accuracy				
Reproducibility: repeatability intermediate precision				
Specificity				
Detection limit				
Quantitation limit				
Linearity				
Range				
Robustness				
Solution stability				

Note: + indicates that the parameter is acceptably tested, – indicates that the parameter is not tested, ? indicates that questions remains before the parameter is judged to be acceptable.

4.5.4. Batch analyses (Section P.5.4)

4.5.5. Characterization of impurities (Section P.5.5)

4.5.6. Justification of specifications (Section P.5.6)

Assessor's comment

4.6. Reference Standards or Materials (Module 3.2.P.6)

Assessor's comment

4.7. Container closure system (Module 3.2.P.7)

Assessor's comment

4.8. Stability (Module 3.2.P.8)

4.8.1. Stability summary and conclusion (Section P.8.1)

Table P. 8-1

Main stability testing

Temperature, °C; Relative humidity (RH), %	n batches x months	Batch size	Package
25 °C / RH 60%		Production scale / Pilot scale	intended for marketing
40 °C / RH 75%			

4.8.2. Post-approval stability protocol and stability commitment (Section P.8.2)

4.8.3. Stability data (Section P.8.3)

The stability data on which the summary and conclusion in P.8.1 is based, is included in the dossier.

4.8.4. Summary of proposed shelf life and storage conditions demonstration for the finished medicinal product

Assessor's comment

5. Appendices (Module 3.2.A)

5.1. Facilities and equipment

5.2. Adventitious agents safety evaluation

5.3. Novel excipients

---

6. Regional information

6.1. Process validation scheme for the finished medicinal product

---

6.2. Medical device issues

6.3. TSE Issues

---

7. Assessor's comments on the SmPC, patient leaflet (package leaflet), and package design

---

8. Assessor's overall conclusions on quality

---

9. List of comments as proposed by the assessor

9.1. Quality aspects

9.2. Major objections

9.2.1. Active substance (related to additional data provided by applicant only)

9.2.2. Active substance (applicant's part as provided by ASMF holder)

Note: In case the ASMF procedure is used the following should be stated in case potential serious risks to public health are being raised on the restricted part of the ASMF: <*for potential serious risks to public health in the restricted part of the ASMF see the separate assessment report on the ASMF*>.

9.2.3. Finished medicinal product

9.3. Other concerns

9.3.1. Active substance (related to additional data provided by applicant only)

Note: When applicable: *<for other concerns on the restricted part of the ASMF, see separate assessment report on the ASMF>*

9.3.2. Finished medicinal product

9.4. Recommendations

---

10. Annex 1 (as appropriate)

(template)

Active Substance Master File

ASSESSMENT REPORT

{Active substance}
{Active substance manufacturer}
{reference number} (where available)
{(Version Number Applicant's part, dated Version Number restricted part), dated}

10.1. Administrative information

Procedure Number:	
INN (or common name) of the active substance(s):	
Active substance manufacturer's Internal API code (if applicable):	
Active substance manufacturer's manufacturing facility(ies) name(s) and address(ses)	Manufacturer's name: Address: Contact person: Telephone: Telefax: E-Mail:
Date of active substance master file Assessment Report	procedure (marketing authorization, variation):

Maximum daily dose	(e.g., < 1 gram, < 10 gram, etc.)
Routes of administration	
Target/patient groups	*<Neonates/infants/children, adults>*

Notes:
1. The structure of the report shall reflect the relevant parts of Module 3.2.S.
2. A separate assessment report is needed for each Active Substance Master File (ASMF).
3. This report will not be sent to the Marketing Authorization Holder but only to the relevant AS manufacturer/holder of the ASMF.
4. Letters of Access in relation to specific drug products are described in the Quality Assessment report for the product in question

10.2. Assessment report and questions on the applicant's part of the ASMF

This Assessment Report solely concerns the ASMF. It should however always be read in conjunction with the assessment report(s) of the Medicinal Product Application for the medicinal product for which it is associated with.

An ASMF in Common Technical Document format has been provided by (ASMF holder) for the (active substance):

S.1 General information

S.2 Manufacture

S.2.1. Manufacturer (name and address of the API manufacturer)

S.2.2. Description of the Manufacturing Process and Process Controls (brief outline)

S.3. Characterization

S.3.1. Elucidation of structure and other characteristics

S.3.2. Impurities

S.4. Control of AS

S.4.1. Specification

S.4.2. Analytical procedure

S.4.3. Validation of analytical procedure

S.4.4. Batch analyses

S.4.5. Justification of specification

S.5. Reference standards or materials

S.6. Container Closure System

S.7. Stability

S.7.1. Stability summary and conclusion

S.7.2. Post-Approval Stability Protocol and Stability Commitments

---

S.7.3. Stability data

OVERALL CONCLUSION
on the applicant's part of the ASMF

LIST OF COMMENTS
on the applicant's part of the ASMF

Major objections:

Other concerns:

ASSESSMENT OF RESPONSES
to the list of questions for the applicant's part of the ASMF

Major objections:

Question_____

Summary of the applicant's response_____

Assessment of the applicant's response_____

Overall summary and conclusion_____

Other concerns:

Question_____

Summary of the applicant's response_____

Assessment of the applicant's response_____

Overall summary and conclusion_____

OVERALL CONCLUSION
on the applicant's part of the ASMF

10.3. Assessment report and questions
on the restricted part of the ASMF

CONFIDENTIAL

THIS SECTION SHOULD NOT BE DISCLOSED TO THE APPLICANT

{reference number } (where available)

{(Version Number applicant's part, dated
Version Number restricted part), dated}

10.4. Administrative information

Procedure Number:	
INN (or common name) of the active	

substance(s):	
Active substance manufacturer's Internal API code (if applicable):	
Active substance manufacturer's manufacturing facility(ies) name(s) and address(ses)	Name: Address: Contact person: Telephone: Telefax: E-Mail:
Date of active substance master file Assessment Report	procedure (marketing authorization, variation):

Note: The structure of the report should reflect the relevant parts of Module 3.2.S.

S.2. Manufacturing

S.2.1. Manufacturer of AS (name, address and responsibility of each party, including contractors/intermediate(s) manufacturer(s) involved in the manufacturing chain)

S.2.2. Description of the manufacturing process and process controls (detailed information)

S.2.3. Control of materials

S.2.4. Control of critical steps and intermediates

S.2.5. Process validation and/or evaluation

S.2.6. Manufacturing process development

S.3. Characterization

S.3.2. Impurities (in accordance with Appendix 10 to the Rules of authorization and assessment of medicinal products for human use in the Eurasian Economic Union subject to approval by the Eurasian Economic Commission (if applicable))

S.4. Control of API

S.4.5. Justification of the specification (in accordance with Appendix 10 to the Rules of authorization and assessment of medicinal products for human use in the Eurasian Economic Union subject to approval by the Eurasian Economic Commission (if applicable)).

OVERALL CONCLUSION
on the restricted part of the ASMF

LIST OF COMMENTS
on the restricted part of the ASMF

Major objections:

Other concerns:

ASSESSMENT OF RESPONSES
to the list of questions on the restricted part of the ASMF

Major objections:

Question_____

Summary of the ASMF holder's response_____

Assessment of the ASMF holder's response_____

Overall summary and conclusion_____

Other concerns:

Question_____

Summary of the ASMF holder's response_____

Assessment of the ASMF holder's response_____

Overall summary and conclusion_____

GENERAL CONCLUSION
on the restricted part of the ASMF

---

11. Annex 2.
Design space and change management protocols (where applicable)

This Annex is an extract of the main body of the AR and its purpose is to summaries all aspects agreed upon in the dossier that result to post approval regulatory flexibility. This annex may be used by Inspectors and could be a basis for the evaluation of post-approval variation applications.

1. Active substance

1.1. Design space for the active substance

Presentation of the Design Space (attributes and their ranges) in a tabular format.

1.2. Change management protocols for the active substance

Description of the changes included in the agreed protocol as well as the agreed variation category for reporting the implementation of the change

2. Finished medicinal product

2.1. Design space for the finished product

Presentation of the Design Space (attributes and their ranges) in a tabular format.

2.2. Change management protocols for the finished medicinal product

Description of the changes included in the agreed protocol as well as the agreed variation category for reporting the implementation of the change.

APPENDIX 9
to the Rules of authorization
and assessment of medicinal products
for human use

NEW ACTIVE SUBSTANCE STATUS TEMPLATE

Completion guide: preset text templates are bracketed in this document using < > and in italics; text template fragments to be filled by entering specific versions of the text on the specified property (parameter) are bracketed in curly brackets using {} with indication of the property (parameter) to be added in italics.

(template)

CRITICAL ASSESSMENT REPORT

on the claim of new active substance (NAPI) status of _____,
(name of active pharmaceutical substance)

contained in _____
(name of the medicinal product)

Assessor:	
Start of the procedure:	
Date of this report:	
Deadline for comments:	

Administrative information

Application number	
Brand name of the medicinal product	
Active pharmaceutical substance	
International non-proprietary name (INN) or common name of the active substance	
Applicant	
Applied Indications	
Pharmaco-therapeutic group (ATC code)	
Pharmaceutical form and strength(s)	
Names of the assessors (internal and external)	Quality: Name: Tel (fax): Email: Non-clinical: Name: Tel (fax): Email: Clinical: Name: Tel (fax): Email:

1. Recommendations

Based on the review of the data the assessor considers that the active substance <active substance> contained in the medicinal product <product name>

<is to be qualified as a new active substance <in itself.> <in comparison to the known <isomer/mixture of isomers/complex /derivative/salt of {INN (salt) approved} previously authorized in the Union as <active substance> it differs significantly in properties with regard to safety and efficacy from the previously authorized substance.>

<could be qualified as a new active substance <in itself> <in comparison to the known <isomer/mixture of isomers/complex /derivative/salt of {INN (salt) approved} previously authorized in the Union as {name of the medicinal product approved}> <provided that satisfactory responses are given to the concerns as detailed in the List of Questions>

<is not to be qualified as a new active substance <in itself.> <in comparison to the known <isomer/mixture of isomers/complex /derivative/salt of {INN (salt) approved} previously authorized in the Union as {name of the medicinal product approved} as it does not differ significantly in properties with regard to safety and efficacy from the previously authorized substance.> The concerns identified, which preclude the recommendation are detailed in the List of Questions.>

2. Executive summary

2.1. Problem statement

This marketing authorization application (MAA) was submitted for review in accordance with the Rules of authorization and assessment of medicinal products for human use in the Eurasian Economic Union and it contained evidence and discussion as to why the active substance <active substance> should be regarded as new.

The applicant requested the active substance <active substance> contained in the above medicinal product to be considered a new active substance <in itself.> <in comparison to the known <isomer/mixture of isomers/complex /derivative/salt of {INN (salt) approved} previously authorized in the Union as {name of the medicinal product approved}, and claimed that <active substance> differs significantly in properties with regard to safety and efficacy from the already authorized substance.>

3. Assessor’s scientific evaluation

3.1. Quality aspects

Discussion on quality aspects

Conclusions on quality aspects

Non-clinical aspects

Discussion on non-clinical aspects

Conclusions on non-clinical aspects

3.2. Clinical aspects

Discussion on clinical aspects

Conclusions on clinical aspects

4. Overall conclusion

[For opinions where further information should be provided by the applicant]

< Based on the review of data on the quality, non-clinical and clinical properties of the active substance, the assessor considers that further evidence should be provided by the applicant to substantiate the claim that <active substance> is to be qualified as a new active substance. Satisfactory answers must be given to the concerns as detailed in the List of Questions.>

[For opinions where no further information should be provided and where the applicant claimed that the compound is a new active substance in itself]

<Based on the review of data on the quality, non-clinical and clinical properties of the active substance, the assessor considers that <active substance> is <not> to be qualified as a new active substance.>

[For opinions where no further information should be provided and where the applicant claimed that the compound is a new active substance in comparison to a known isomer/mixture of isomers/complex /derivative/salt of a chemical substance previously authorized as a medicinal product in the Eurasian Economic Union]

<Based on the review of data on the quality, non-clinical and clinical properties of the active substance, the assessor considers that <isomer/mixture of isomers/complex /derivative/salt of> {INN (+salt) applicant} in comparison to the known <isomer/mixture of isomers/complex /derivative/salt of> {INN (salt) approved} is <not> to be qualified as a new active substance as it <differs><does not differ> significantly in properties with regard to safety and efficacy from the previously authorized substance.>

5. List of questions

APPENDIX 10
to the Rules of authorization
and assessment of medicinal products
for human use

Active Substance Master File Procedure

I. INTRODUCTION (BACKGROUND)

The main objective of the Active Substance Master File (ASMF) procedure is to allow valuable confidential intellectual property or 'know-how' of the manufacturer of the active substance (ASM) to be protected, while at the same time allowing the Applicant or Marketing Authorization holder (MAH) to take full responsibility for the medicinal product and the quality and quality control of the active substance. Competent Authorities of the Member States thus have access to the complete information that is necessary for an evaluation of the suitability of the use of the active substance in the medicinal product.

II. SCOPE

This Appendix is intended to assist Applicants/MA holders in the compilation of the active substance section of their dossiers for a Marketing Authorization Application (MAA) or a Marketing Authorization Variation (MAV) of a medicinal product (Section 3.2.S). It is also intended to help ASMF holders in the compilation of their ASMFs.

III. CONTENT OF THE ACTIVE SUBSTANCE MASTER FILE

ASMFs linked to human medicinal products should be presented in the format of the Common Technical Document (CTD), see table 1.

The scientific information in the ASMF should be physically divided into two separate parts, namely the Applicant's Part (AP) and the Restricted Part (RP). The AP contains the information that the ASMF holder regards as non-confidential to the Applicant/MAH, whereas the RP contains the information that the ASMF holder regards as confidential, see Annex 1. It is emphasized that the AP is still a confidential document that cannot be submitted by anyone to third parties without the written consent of the ASMF holder. In all cases the AP should contain sufficient information to enable the Applicant/MAH to take full responsibility for an evaluation of the suitability of the specification for the active substance to control the quality of this active substance for use in the manufacture of a specified medicinal product.

The RP may contain the remaining information, such as detailed information on the individual steps of the manufacturing method (reaction conditions, temperature, validation and evaluation data of critical steps) and the quality control during the manufacture of the active substance. The Competent Authorities of the Member States may not accept that particular information has not been disclosed to the Applicant/MAH. In such cases, the Competent Authorities of the Member States may ask for an amendment to the AP.

In addition to the AP and RP, the ASMF should contain a table of contents, and separate summaries for both the AP and the RP. In Each version of the AP and RP should have unique and independent version control numbers.

IV. USE OF THE ACTIVE SUBSTANCE MASTER FILE PROCEDURE

An ASMF can only be submitted in support of an MAA or MAV in the Union. The relationship between the quality of the active substance and its use in the medicinal product needs to be justified in this MAA or MAV.

Although the ASMF procedure is developed to keep intellectual property of the ASM confidential, it is also permissible to use the procedure when there is no confidentiality issue between the Applicant/MAH and the ASM (e.g. when the Applicant/MAH synthesizes the active substance himself). It is expected that the ASM is also the holder of the ASMF.

The ASMF procedure can be used for the following active substances, including herbal active substances/preparations. i.e.:

- New active substances;
- Existing active substances not included in the Pharmacopoeia of the Union or the pharmacopoeia of a Member State;
- Pharmacopeial active substances included in the Pharmacopoeia of the Union or in the pharmacopoeia of a Member State.

The ASMF procedure cannot be used for biological active substances, see Annex 5.

The ASMF holder may have an ASMF as well as a Certificate of Suitability (CEP) issued for a single active substance. Generally, it is however not acceptable that the Applicant/MAH refers to an ASMF as well as to a CEP for a single active substance of a particular MAA/MAV. In cases where the CEP contains too little information (e.g. stability) the Competent Authorities of the Member States may decide that additional information should be provided in the dossier. In such case it may be acceptable to refer both to an ASMF and a CEP.

The ASMF holder should give permission to the Competent Authorities of the Member States to assess the data in the ASMF in relation to a specific MAA/MAV, in the form of a 'Letter of Access', see Annex 2.

The ASMF holder should submit to the Applicant/MAH:

• a copy of the latest version of the AP (and, if applicable, responses to deficiency letters on the AP from a Competent Authority of the Member State if not already incorporated into the AP);

• a copy of the QOS or detailed and critical summary, as appropriate, on the latest version of the AP;

• a copy of the Letter of Access where this letter has not been submitted earlier for the product concerned.

In addition, it is an essential requirement that the ASMF holder should submit to all Competent Authorities of the Member States involved in the MAA/MAV procedure:

• the ASMF (and, if applicable, responses to deficiency letters from a Competent Authority of the Member State if not already incorporated into the ASMF), accompanied by a Submission Letter and Administrative Details, see Annex 3. This also applies to the ASMF holder's responses to deficiency letters from a Competent Authority of the Member State;

• the Letter of Access where this letter has not been submitted earlier for the product concerned.

The ASMF holder should submit the ASMF to the Competent Authority of the Member State either for each MAA and each MAV or only once according to national requirements. The submission of the relevant documentation by the ASMF holder to the Competent Authority of the Member State must be synchronized to arrive at approximately the same time as the MAA or the MAV i.e. not more than one month before and not after the intended MAA/MAV submission date.

Where the ASMF procedure is used, the Applicant/MAH should submit the MAA or MAV to the Competent Authorities of the Member States together with the Letter of Access where this Letter has not been submitted earlier by the MA holder/Applicant himself or by the ASMF holder for the product concerned.

Where the same active substance is used in a number of applications for different products in one or more Member States, the ASMF holder should submit identical documentation to every Competent Authority of the Member State. Consequently, the Competent Authorities of the Member States may require that any ASMF updates made in relation to one MA should apply to all. It is the ASMF holder's responsibility to notify the MA holders and Competent Authorities of the Member States concerned about any changes to the AP and/or RP, so that the MAHs can update all affected MAs accordingly.

V. CONTENT OF THE MARKETING AUTHORIZATION APPLICATION DOSSIER WHEN THE ACTIVE SUBSTANCE MASTER FILE PROCEDURE IS USED

The Applicant/MAH is responsible for ensuring that he has access to all relevant information concerning the current manufacture of the active substance.

The specification used by the Applicant/MAH to control the correct quality of the active substance should be laid down unambiguously in the marketing authorization application dossier (CTD format section 3.2.S.4.1 and 3.2.S.4.2). The Applicant/MAH should include a copy of the AP in the marketing authorization application dossier (CTD format section 3.2.S). The version of the AP in the marketing authorization application dossier should be the most recent and it should be identical to the AP as supplied by the ASMF holder to the Competent Authority of the Member State as part of the ASMF. The Applicant/MAH should include all relevant details from the AP in the QOS/detailed and critical summary of the marketing authorization application dossier. Issues of the ASMF that are specifically relevant to the product under consideration should be highlighted in the QOS/detailed and critical summary of the marketing authorization application dossier.

In the case of a single supplier and where the ASMF procedure or CEP procedure is used, the specification for the active substance provided by the Applicant/MAH in the marketing authorization application dossier should in principle be identical to that of the ASMF holder or the CEP holder. However, the Applicant/MAH does not need to accept redundant tests in the specification, unnecessarily tight specification limits or outdated analytical methods.

In cases where the Applicant/MAH uses a different analytical method than that described in the ASMF, both methods should be validated. Technical tests in the specification that are relevant for the medicinal product, but which are normally not part of the specification in the ASMF (e.g. particle size), should be part of the specification of the Applicant/MAH.

In cases where there is more than one supplier, the Applicant/MAH should have one single compiled specification that is identical for each supplier. It is acceptable to lay down in the specification more than one acceptance criterion and/or analytical method for a single parameter with the statement 'if tested' (e.g. in case of residual solvents).

VI. CHANGES AND UPDATES TO THE ACTIVE SUBSTANCE MASTER FILE

As for medicinal products, ASMF holders should keep the content of their ASMFs updated with respect to the actual synthesis/manufacturing process. The quality control methods should be kept in line with the current regulatory and scientific requirements.

ASMF holders shall not modify the contents of their ASMF (e.g. manufacturing process or specifications) without informing each Applicant/MAH and each Competent Authority of the Member State. This obligation remains valid until the Letter of Access has been withdrawn by

the ASMF holder, see Annex 4. ASMF holders should provide the updated ASMF to all interested parties with reference to the revised version number.

Any change to the ASMF should be reported by every MAH to the relevant Competent Authority of the Member State by means of an appropriate variation procedure. A Submission Letter should be provided (Annex 3).

In cases where the contents of the ASMF cannot be changed for a certain period of time because of other procedural provisions (i.e. mainly because of on-going MRP procedures), the ASMF holder should still provide the aforementioned data to the MAH and Competent Authorities of the Member States making reference to this reason and requesting a later date of implementation.

At the occasion of the 5-year renewal of a medicinal product, MAHs are required to declare that the quality of the product, in respect of the methods of preparation and control, has been regularly updated by variation procedure to take account of technical and scientific progress, and that the product conforms with current Union quality guidelines. They will also declare that no changes have been made to the product particulars other than those approved by the Competent Authority of the Member State.

MAHs should therefore verify with their ASMF holders whether the above declaration can be met in respect to the active substance particulars. In case changes have not been notified to the MAH and Competent Authority of the Member State, the necessary variation procedure should be initiated without delay.

Annex 1

Overview ASMF contents

Table 1

Table 1	CTD format	Applicant's Part	Restricted Part
3.2.S.1	General information	x	
3.2.S.1.1	Nomenclature	x	
3.2.S.1.2	Structure	x	
3.2.S.1.3	General properties	x	
3.2.S.2	Manufacture	x	x
3.2.S.2.1	Manufacturer(s) Including all companies involved in the manufacture of the active substance, including quality control/ in process testing sites, intermediate manufacturers, milling and sterilization sites.	x	
3.2.S.2.2	Description of Manufacturing Process and Process controls	1	2
3.2.S.2.3	Control of Materials		x
3.2.S.2.4	Control of critical steps and intermediates	3	4
3.2.S.2.5	Process validation and/or Evaluation		x
3.2.S.2.6	Manufacturing Process Development		x
3.2.S.3	Characterization	x	
3.2.S.3.1	Elucidation of Structure and other Characteristics	x	
3.2.S.3.2	Impurities	x	5
3.2.S.4	Quality Control of Active Substance	x	
3.2.S.4.1	Specification	x	
3.2.S.4.2	Analytical procedures	x	
3.2.S.4.3	Validation of analytical procedures	x	
3.2.S.4.4	Batch analysis	x	
3.2.S.4.5	Justification of specification	x	6
3.2.S.5	Reference standards or materials	x	
3.2.S.6	Container Closure System	x	
3.2.S.7	Stability	x	
3.2.S.7.1	Stability summary and conclusion	x	
3.2.S.7.2	Post-approval Stability Protocol and Stability Commitment	x	
3.2.S.7.3	Stability data	x	

1. Flow chart and short description is regarded as sufficient, if detailed information is presented in the Restricted

Part. However, full validation data on the sterilization process may be requested in the Applicant's Part (in cases where there is no further sterilization of the final product).

2. Detailed information.

3. As far as the information is also relevant for the Applicant/MAH.

4. As far as the information is related to the detailed description of the manufacturing process and as far as this information is not relevant for the Applicant/MA holder.

5. In so far as the information is related to the detailed description of the manufacturing process and in so far as the ASMF holder sufficiently justifies that there is no need to control these impurities in the final active substance.

6. As far as the information is related to the detailed description of the manufacturing process, control of materials and process validation.

Table 2

Section	CTD format Herbal Active Substances	Applicant's Part	Restricted Part
3.2.S.1	General information	x	
3.2.S.1.1	Nomenclature A) For herbal substance: • Binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable) • Parts of the plants • Definition of the herbal substance • Other names (synonyms mentioned in other Pharmacopoeias) • Origin (wild or cultivated) B) For herbal preparations • Binomial scientific name of plant (genus, species, variety and author), and chemotype (where applicable) • Parts of the plants • Definition of the herbal preparation • Ratio of the herbal substance to the herbal preparation • Extraction solvent(s) • Other names (synonyms mentioned in other Pharmacopoeias) • Origin (wild or cultivated)	x	
3.2.S.1.2	Structure - Physical form - Description of the constituents with known therapeutic activity or markers (molecular formula, relative molecular mass, structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass). - Other constituent(s)	x	
3.2.S.1.3	General properties	x	
3.2.S.2	Manufacturer(s):		

	For herbal substances The name, address, and responsibility of each supplier, including contractors, each proposed site or facility involved in production/collection and testing of the herbal substance should be provided, where appropriate.		x
	For herbal preparations The name, address, and responsibility of each manufacturer, including contractors, and each proposed manufacturing site or facility involved in manufacturing and testing of the herbal preparation should be provided, where appropriate.	x	
3.2.S.2.2	Description of critical steps and intermediates	Flow chart	Detailed information
	For herbal substances Information should be provided to adequately describe the plant production and plant collection, including: • Geographical source of medicinal plant • Cultivation, harvesting, drying and storage conditions • Batch size For herbal preparations Information should be provided to adequately describe the manufacturing process of the herbal preparation, including: • Description of processing (incl. flow-chat • Solvents, reagents • Purification stages • Standardization • Batch size		
3.2.S.2.3	Control of materials		x
3.2.S.2.4	Control of critical steps and intermediates	If also relevant for the MA holder/applicant	x
3.2.S.2.5	Process validation and/or evaluation	x	x

3.2.S.2.6	Manufacturing Process Development		x
	A brief summary describing the development of the herbal substance(s) and herbal preparation(s) where applicable should be provided, taking into consideration the proposed route of administration and usage. Results comparing the phytochemical composition of the herbal substance(s) and herbal preparation(s) where applicable used in supporting bibliographic data and the herbal substance(s) and herbal preparation(s) where applicable described in S1 should be discussed, where appropriate.		
3.2.S.3	Characterization	x	
3.2.S.3.1	Elucidation of structure and other characteristics	x	
	For herbal substances		
	Information on the botanical, macroscopical, microscopical, phytochemical characterization, and biological activity if necessary, should be provided:		
	For herbal preparations		
	Information on the phyto- and physicochemical characterization, and biological activity if necessary, should be provided:		
3.2.S.3.2	Impurities	x	
3.2.S.4	Control of drug substance	x	
3.2.S.4.1	Specification	x	
3.2.S.4.2	Analytical procedure	x	
3.2.S.4.3	Validation of analytical procedure	x	
3.2.S.4.4	Batch analysis	x	
3.2.S.4.5	Justification of specification	x	x
3.2.S.5	Reference standards of materials	x	
3.2.S.6	Container closure system	x	
3.2.S.7	Stability	x	
3.2.S.7.1	Stability summary and conclusion	x	
3.2.S.7.2	Post-approval stability protocol and stability commitment	x	
3.2.S.7.3	Stability data	x	

Annex 2

TEMPLATE LETTER OF ACCESS TO RESTRICTED PART OF ASMF

(< FROM ACTIVE SUBSTANCE MASTER FILE HOLDER ON HEADED PAPER>)

[Address of Competent Authority of the Member State]

[Date]

Number of Active Substance Master File:

<ASMF reference number>

The following format shall be used: EAEU/ASMF/XXXXX or YY/ASMF/XXXXX where XXXXX 5-digit number, YY 2-letter code of the Member State

Name of Active Substance:

Internal API Code (if applicable):

Active Substance Master File holder: [name and address]

The aforementioned Active Substance Master File holder hereby authorizes the <name of Competent Authority of the Member State> to refer to and review the above mentioned Active Substance Master File in support of the following Marketing Authorization Application(s) or Marketing Authorization Variation(s) submitted by [Name of Marketing Authorization Holder/Applicant] on [planned date of submission]:

[Name of product and Marketing Authorization number (if known)]

If no Brand name has been agreed at the time of submission for this product: it should be indicated ‘INN + Marketing Authorization Holder name’

[Name of Applicant or Marketing Authorization holder]

The aforementioned Active Substance Master File holder commits to ensure batch to batch consistency and to inform [Name of Marketing Authorization Holder/Applicant] and Competent Authority of the Member State of any change in the Active Substance Master File.

The aforementioned Active Substance Master File holder hereby is informed of and accepts that the Competent Authorities of the Member States may share the assessment reports of the above mentioned Active Substance Master File amongst themselves.

Signature for the Active Substance Master File holder

[Name and function]

[Signature]

Annex 3

Template Submission Letter and Administrative Details for documents relating to an Active Substance Master File (ASMF)

To be submitted together with the ASMF in conjunction with every MAA/variation submission as one document

(< FROM ACTIVE SUBSTANCE MASTER FILE HOLDER ON HEADED PAPER>)

From:<ASMF Holder name>
<ASMF Holder address>
<ASMF Holder Country>

To: <Name and Address of Competent Authority>
<Date>
<Reference>

Subject: Submission of documents relating to an ASMF
for <Name of Active Substance> - < ASMF reference number>

The following format shall be used: EAEU/ASMF/XXXXX or YY/ASMF/XXXXX where XXXXX 5-digit number, YY 2-letter code of the Member State

Dear Sir or Madam:

This Active Substance Master File is submitted in relation to the following product:

Medicinal product	<Name of the medicinal product>
Allocated procedure number (as applicable)	If no Brand name has been agreed at the time of submission for this product: it should be indicated 'INN + Marketing Authorization Holder name'
(Intended) Submission date of the marketing authorization application or variation (if known)	< procedure reference> <DD/MM/YYYY>

Administrative details for documents relating to an Active Substance Master file (ASMF)

This submission letter should be used for an Active Substance Master File to be assessed in conjunction with a marketing authorization application or variation for medicinal product. It is mandatory to complete all information fields

This submission is also sent to:	□ All participating Member States □ <reference Member State> only

ASMF reference number	<ASMF reference number> The following format shall be used: EAEU/ASMF/XXXXX or YY/ASMF/XXXXX where XXXXX 5-digit number, YY 2-letter code of the Member State
ASMF holder's version (as included in this submission)	Applicants part: Version [version number]/date (dd-mm-yyyy) Restricted part: Version [version number]/date (dd-mm-yyyy)
Active substance name	<INN, common name> (+ salt/water content when applicable)
Active Substance Manufacturer's internal API code (if applicable):	<API internal code>
Additional information (as applicable, e.g. different route of synthesis, grade) Applicable when an ASMF holder has more than one ASMF for the same active substance.	

ASMF Holder	<ASMF Holder name> <Full ASMF Holder administrative address> <Country> Contact person: <name> Telephone: <telephone No.> e-mail: <e-mail>
Active Substance Manufacturer Manufacturing site(s) (All companies involved in the manufacture of the active substance, including quality control / in process testing sites, intermediate manufacturers, milling and sterilization sites should be listed in separate boxes.)	<Manufacturing site address(es)> <Country> <D-U-N-S number> A Data Universal Numbering System (D-U-N-S) for all manufacturing sites should be provided, if registered. The D-U-N-S system was developed by Dun & Bradstreet (D&B) which assigns a unique digit numeric identifier to a single business entity. It is used in this case to facilitate the identification of manufacturing sites outside of the Union <GPS (WGS 84) coordinates of the site> Latitude (S or N) and Longitude (E or W) expressed in Degrees Minutes Seconds to 1 decimal place (Alternatively it can be expressed in Degrees to at least 5 decimal places or Degrees Minutes to at least 3 decimal places). If not main entrance, specify site. Contact person: <name> Telephone: <telephone No.> e-mail: <e-mail>

Submission Type	□ New submission □ Update to the ASMF □ Response to deficiency letter (both Applicant's and Restricted Parts, where applicable) □ Administrative change only (manufacturing site remains unchanged in all cases) □ Change of ASMF holder □ Change of name/address of ASMF holder □ Change of name/address of Active substance manufacturer

Submission Format	□ paper submission □ electronic format (paper submissions will not be accepted when electronic format is submitted)
Number of Volumes of Paper Copy	<Number>
Number of Media Units	<Number>

Submitted Documents	□ Letter of Access (see Annex 2) □ A copy of the Expert's curriculum vitae □ QOS or detailed and critical summary, as appropriate □ Table of Changes (only for submission of an update to a currently authorized ASMF) □ A copy of the proposed ASMF holder's active substance specification □ A copy of the ASMF Deficiency Letter sent by Competent Authority of the Member State (only for submission of response documents)

Table of Changes between different versions of the ASMF

This section should only be completed for updates to an already submitted ASMF.

The Table of Changes should be included as a separate document to the main Submission Cover Letter. The ASMF holder should use the following example templates for the table. If the changes have been previously authorized by other Competent Authority of the Member State, the ASMF holder should annotate the table with the procedure number.

Table of Changes example template

TABLE OF CHANGES		
	PRESENT	PROPOSED
	ASMF holder's RP and/or AP Version Number [version number]/date (dd-mm-yyyy)	ASMF holder's RP and/or AP Version Number [version number]/date (dd-mm-yyyy)
CTD Section	Current situation	Description of change

Administrative Information In Relation To Other Marketing Applications/Authorizations Dossiers

Other Applications/Authorizations referring to the same ASMF

The ASMF has previously been submitted to a Competent Authority of the Member State	Yes ☐
	No ☐

If yes, please provide a list of medicinal products containing the drug substance manufactured in accordance with the details submitted in the ASMF. Use additional sheets if necessary. Include the 5 most recently submitted medicinal products or all medicinal products submitted within the last 2 years, whichever is greater.

Procedure Reference Number	ASMF Number	ASMF holder's Version Number (RP & AP)/Date

More information may be submitted by the ASMF holder. Information on additional medicinal products concerned by this ASMF may be requested by the competent authorities

[Signature of the authorized contact person]

[Name, address and position]

Annex 4

TEMPLATE WITHDRAWAL OF ACCESS LETTER TO RESTRICTED PART OF ASMF

(< FROM ACTIVE SUBSTANCE MASTER FILE HOLDER ON HEADED PAPER>)

[Address of Competent Authority of the Member State]

[Date]

Number of Active Substance Master File:

<ASMF Reference number>

The following format shall be used: EAEU/ASMF/XXXXX or YY/ASMF/XXXXX where XXXXX 5-digit number, YY 2-letter code of the Member State

Name of Active Substance:

Internal API Code (if applicable):

Active Substance Master File holder: [name and address]

The aforementioned Active Substance Master File holder hereby informs the <name of Competent Authority of the Member State> that they no longer wish the above Active Substance Master File to be used in support of the following Marketing Authorization Application, held by [Name of Marketing Authorization Holder/Applicant] (Separate Letters of Withdrawal should be submitted for different Marketing Authorization Holders / Applicants):

Medicinal product	<Name of the medicinal product>
Allocated procedure number (as applicable)	If a Marketing Authorization has not been granted for the product and an Brand name not agreed at the time of submission for this product: it should be indicated 'INN + Marketing Authorization Holder name' <product reference number/procedure reference>

The aforementioned Active Substance Master File holder hereby confirms that they have previously informed [Name of Marketing Authorization Holder/Applicant] of this decision in line with the terms of their supply agreement.

□ Active Substance manufactured in accordance with the above Active Substance Master File will no longer be supplied after [supply agreement termination date],

□ Replacement of the Active Substance Master File by Certificate of Suitability, [CEP no]. A copy of the Certificate of Suitability is attached to this letter

Signature of the Active Substance Master File holder

[Name and function]

[Signature]

Annex 5

Non-applicability of the Active Substance Master File (ASMF) concept

1. Non applicability of Active Substance Master File (ASMF) concept to biological active substances

Marketing Authorization Holders (MAH) and Applicants are advised that the concept of Active Substance Master Files cannot be applied in the context of biological medicinal products.

The characterization and determination of biological active substances' quality requires not only a combination of physicochemical and biological testing, but also extensive knowledge of the production process and its control.

The MAH/applicant for a biological medicinal product could therefore not comply with the requirement to 'take responsibility for the medicinal product' without having full and transparent access to these quality-related data. The use of an ASMF would prevent such access, and should therefore not be allowed for biological active substances.

In addition, active substances, which are present in certain medicinal products such as vaccines or cell-therapy medicinal products, do not fit with the concept of a 'well-defined' active substance.

2. Non-applicability of ASMF concept of open and closed parts to Vaccine Antigen Master File (VAMF) and Plasma Master File (PMF)

The legislation does not provide for the use of open/closed parts in the Vaccine Antigen Master File (VAMF) and Plasma Master File (PMF). The concept of open (non-confidential) and closed (confidential) parts is specific to the Active Substance Master File.

Regarding the VAMF the legislation specifies that the VAMF holder cannot differ from the MAH/applicant for the concerned medicinal product: there is hence no rationale for an 'open/closed' parts system.

For the PMF the legislation specifies that where the MAH/applicant differs from the holder of the PMF, the PMF shall be made available to the MAH/applicant for submission to the Competent Authority of the Member State.

Annex 6

Glossary

For the purposes of this Appendix, the following terms shall bear the following meanings:

Active Substance Manufacturer - A party involved in the manufacturing chain of the active substance, including agents, brokers, traders, distributors, repackers or relabellers.

Active Substance Master File holder- This is the company that has the ultimate responsibility for the Active Substance Master File.

Manufacturing chain - A clear flow chart or written text explaining the manufacturing and distribution route of the active substance from the first starting materials to the final active substance as delivered to the Applicant/Marketing Authorization holder.

New active substance - The designated therapeutic moiety, which has not previously been registered in a region or Member State (also referred to as a new molecular entity or new chemical entity). It may be a complex, simple ester, or salt of a previously approved drug substance.

APPENDIX 11
to the Rules of authorization
and assessment of medicinal products
for human use

PRELIMINARY SUMMARY REPORT TEMPLATE

Completion guide: preset text templates are bracketed in this document using < > and in italics; text template fragments to be filled by entering specific versions of the text on the specified property (parameter) are bracketed in curly brackets using {} with indication of the property (parameter) to be added in italics.

(template)

PRELIMINARY SUMMARY ASSESSMENT REPORT
on a Medicinal Product

<Brand name>
<(Active substance(s))>
Applicant:

Start of the procedure:	
Date of this report:	
Deadline for comments:	

I. ADMINISTRATIVE INFORMATION

Application number:	
Brand name of the medicinal product:	
International Non-proprietary Name (INN) or common name of active substance(s):	
Applicant:	
Applied Indications:	
Pharmaco-therapeutic group (ATC code):	
Pharmaceutical form and strength(s):	
Names of the Rapporteur assessors (internal and external):	Quality: Name: Tel (fax): Email: Non-clinical: Name: Tel (fax): Email: Clinical: Name: Tel (fax): Email:
<In accordance with the Rules of authorization and assessment of medicinal products for human use of the Union, it is hereby declared that I have completed the assessment report in less than 80 days>	date signature

List of abbreviations

Recommendation

Based on the assessors' reviews of the data on quality, safety and efficacy contained in the MAA, the assessors consider that the application for <product name> in the treatment of *<claimed therapeutic indications>,*

<can be approvable provided that satisfactory answers are given to the preliminary list of other concerns (Section V)> <is not approvable since major objections have been identifiedб which preclude a recommendation for marketing authorization at the present time. The details of these major objections are provided in the preliminary list of questions (Section V)>.

<The major objections precluding a recommendation for marketing authorization pertain to the following principal deficiencies: <summarize the deficiencies from Section VI Conclusions>>.

Questions to be posed by additional assessors

Provide a list of questions

Requests for inspections

Inspection(s) for compliance with the Rules of the Good Manufacturing Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission (GMP).

[For routine GMP inspections]

<A request for a GMP inspection has been adopted for the following sites in order to verify their GMP compliance status due to the expiration of the current site certificate of compliance. The outcome of these inspections is required to complete the examination of the application and will be needed by Day 181.>

[For initiated GMP inspections]

<A request for a GMP inspection has been adopted for the following sites in order to verify GMP compliance status in accordance with the criteria for inspection triggering as laid down in the Rules of authorization and assessment of medicinal products for human use subject to approval by the Eurasian Economic Commission. The outcome these inspections is required to complete the examination of the application and will be needed by Day 181.>

Inspection(s) for compliance with the Rules of the Good Clinical Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission (GCP).

<A request for a GCP inspection has been adopted for the following clinical studies <specify study numbers> in accordance with the criteria for inspection triggering as laid down in the Rules of authorization and assessment of medicinal products for human use subject to approval by the Eurasian Economic Commission. The outcome of this inspection and satisfactory responses to its findings are part of the responses to the List of Questions and will be submitted by Day 121.>

<New active substance status>

Based on a review of the data, the assessors consider that the active substance <active substance> contained in the medicinal product <medicinal product>

<is to be qualified as a new active substance <in itself> <in comparison to known <isomer (mixture of isomers/complex /derivative/salt)> previously authorized in the Union as a medicinal product approved as it differs significantly in properties with regard to safety and efficacy from the previously authorized substance.>

<could be qualified as a new active substance <in itself> <in comparison to known <isomer (mixture of isomers/complex/derivative/salt> previously authorized in the Union as a medicinal product, provided that satisfactory responses are given to the concerns as detailed in the List of Questions>

<is not to be qualified as a new active substance <in itself> <in comparison to known <isomer (mixture of isomers/complex/derivative/salt)> previously authorized in the Union as a medicinal product, as it does not differ significantly in properties with regard to safety and efficacy from the previously authorized substance.> Major objections which preclude a recommendation for authorization of this substance as a new AS are detailed in the List of Questions.>.

II. EXECUTIVE SUMMARY

1. Introduction
2. Summary of the Product Characteristics
3. Development program assessment, compliance with the medicinal product development guidance/scientific advice
4. General comments on compliance with the GMP, GLP, GCP
5. The type of application and other comments on the submitted dossier:
   - Legal basis;
   - Conditional approval;
   - Biosimilarity;
   - Significance of paediatric studies.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

1.1. Introduction

1.2. Quality aspects

1.3. General quality issues

1.4. Active substance (API)
- 1.4.1. General information
- 1.4.2.Manufacturing, characterization, and control process
- 1.4.3.Specification
- 1.4.4. Stability
- 1.4.5. Comparability exercise for Active Substance

1.5. Finished Medicinal Product
- 1.5.1. Description of the product and pharmaceutical development
- 1.5.2. Manufacture of the product and process controls
- 1.5.3.Product specification
- 1.5.4. Justification of the shelf life and storage conditions for the medicinal product based on stability testing
- 1.5.5. Comparability exercise for Finished Medicinal Drug Product
- 1.5.6. Adventitious agents
- 1.5.7. GMO

1.6. Discussion on chemical, pharmaceutical, and biological aspects

1.7. Conclusions on chemical, pharmaceutical, and biological aspects

1.8. Non-clinical aspects

1.9. Pharmacology

1.10. Pharmacokinetics

1.11. Toxicology

1.12. Discussion on preclinical aspects

1.13. Conclusions on preclinical aspects

1.14. Clinical aspects
Tabular overview of clinical studies

1.15. Pharmacokinetics

1.16. Pharmacodynamics

1.17. Discussion on clinical pharmacology

1.18 Conclusions on clinical pharmacology

1.19. Clinical efficacy
Dose-response studies and main clinical trials
Summary of the main efficacy results

The following tables summarize the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table {number}

Summary of efficacy for trial <trial>

Title {as indicated in the trial report}	
Study identifier	*<code>* *{list all codes starting with the protocol number followed by – as available - EudraCT number, ISRCT number, other codes that allow cross-referencing to publications}*
Study design	*<free text> {describe key elements of the design (cross-over, parallel, factorial, dose-escalation, fixed-dose response) including randomization, blinding, allocation concealment, mono-/multi-center, etc.}*

	duration of the main phase: duration of the run-in phase: duration of the extension phase:	*<time>* *<time> <not applicable>* *<time> <not applicable>*
Hypothesis	*<Superiority> <Equivalence> <Non-inferiority> <Exploratory: specify>*	
Treatment groups *{add as many rows as needed to describe the treatment groups}*	*<group descriptor>* *{provide an abbreviation for later use in the table of the results section}*	*<treatment>, <duration>, <number of randomized subjects>*
	<group descriptor>	*<treatment>, <duration>, <number of randomized subjects>*
	<group descriptor>	*<treatment>, <duration>, <number of randomized subjects>*

Endpoints *{add as many rows as needed to describe the endpoints; for the secondary endpoints select the ones considered most relevant and reported in the results section}*	*Co-primary endpoint*	*<label>* *{generate abbreviation for later use in the table of the results section}*	*<free text>* *{provide brief description}*
	<Secondary> *<other: specify>* endpoint	*<label>*	*<free text {provide brief description}*
	<Secondary> *<other: specify>* endpoint	*<label>*	*<free text {provide brief description}*
Database lock	<date>		

Results and analysis

{present the result separate for each analysis that is considered relevant for the conclusion on the trial; in any case the pre-specified primary analysis should be presented}

Analysis description	Primary analysis			
Analysis population and time point description	<Intent to treat> <Per protocol> <other: specify> {consider adding a brief description of the definition of the population} <time point>			
Descriptive statistics and estimated variability	Treatment group	*<group descriptor> {as per above terminology}*	*<group descriptor> {as per above terminology}*	*<group descriptor> {as per above terminology}*
	Number of subjects	<n>	<n>	<n>

	<endpoint> {label as above} (<statistic>) {e.g. sample mean, median, etc.}	*<point estimate>*	*<point estimate>*	*<point estimate>*
	<variability statistic> *{e.g. standard deviation, confidence interval, etc.}*	*<variability>*	*<variability>*	*<variability>*
	<endpoint> (<statistic>)	*<point estimate>*	*<point estimate>*	*<point estimate>*
	<variability statistic>	*<variability>*	*<variability>*	*<variability>*
	<endpoint>	*<point estimate>*	*<point estimate>*	*<point estimate>*
	(<statistic>) <variability statistic>	*<variability>*	*<variability>*	*<variability>*
Effect estimate per comparison *{add as many rows as needed to describe the relevant statistical testing performed}*	*co-primary endpoint*	Comparison groups		*<group descriptor> {as per above terminology}*
		<test statistic> {e.g. difference between groups}		*<point estimate>*
		<variability statistic> {e.g. confidence interval, etc.}		*<variability>*
		P-value *{indicate statistical test used, e.g. ANOVA}*		*<P-value>*
	<<Co->Primary> *<Secondary>* *<other: specify>* endpoint	Comparison groups		*<group descriptor>*
		<test statistic>		*<point estimate>*
		<variability statistics>		*<variability>*
	{*specify endpoint*	*<P-value>*		*<P-value>*
	indicate the endpoint using the terminology in the Endpoints and Definitions Section			
	<<Co->Primary> *<Secondary>*	Comparison groups		*<group descriptor>*
		<test statistic>		*<point estimate>*

	<other: specify> endpoint	*<variability statistic>*	*<variability>*
		<P-value>	*<P-value>*
Notes	*<free text>* *{consider amongst others the following information:* *reasons for drop-outs* *critical findings with regard to the analysis}*		
Analysis description	*<secondary analysis>* *<Co-primary Analysis>,<other, specify:>* *{also indicate if the conduct of the analysis was pre-specified}*		
{repeat all the above sections for each analysis that is considered relevant}			

Clinical trials in special populations
Analysis performed across all trials (pooled analyzes and meta-analysis).
Supporting study(ies)

1.20. Assessment on clinical efficacy
Design and conduct of clinical studies
Efficacy data and additional analyzes

1.21. Conclusions on clinical efficacy

1.22. Clinical safety
Patient exposure
Adverse events
Serious adverse events and deaths
Laboratory findings
Safety in special populations
Immunological events
Safety related to drug-drug interactions and other interactions
Discontinuation due to serious adverse events
Discussion on clinical safety
Conclusions on clinical safety

IV. PHARMACOVIGILANCE SYSTEM

<The assessors consider that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Eurasian Economic Union or in a third country.>

< The assessor considers that the Pharmacovigilance system as described by the applicant has the following deficiencies: <list of deficiencies.>

<Provided that the deficiencies are rectified prior to the applicant placing the medicinal product on the market, the assessment organization may consider that the Pharmacovigilance

system will fulfil the requirements. The applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.>

1. **Risk management plan.**

Issues and/or concerns for consideration by the pharmacovigilance assessor when assessing the RMP.

2. **Medicinal products that can have a significant effect in rare, life-threatening, or debilitating diseases.**

<According to the conclusion of the competent authority (Opinion dated <date>) the prevalence of the "condition" <state the condition> is <state prevalence> per 10 000 individuals in <Member State.>

<(N/A)>

3. **Risk-benefit assessment**

Benefits
Beneficial effects
Uncertainty in the knowledge about the beneficial effects
Risks
Unfavorable effects
Uncertainty in the knowledge about the unfavorable effects
Risk-benefit balance
Importance of favorable and unfavorable effects
Risk-benefit balance
Discussion on the risk-benefit balance

4. Conclusions

The overall risk-benefit balance of *<name of medicinal product>* is *<positive>*, *<positive>*, provided *<general statement on conditions>*; *<negative>*.

V. LIST OF ASSESSORS' QUESTIONS

1. Module 3 (Quality aspects)

Major objections:
Active substance
Finished medicinal product
Other concerns:
Active substance
Finished medicinal product
Recommendations

2. Module 4 (Preclinical aspects).

Major objections:
Pharmacology
Pharmacokinetics
Toxicology
Other concerns:
Pharmacology
Pharmacokinetics
Toxicology

Recommendations

3. Module 5 (Clinical aspects).

Major objections:
Pharmacokinetics
Pharmacodynamics
Clinical efficacy
Clinical safety
Pharmacovigilance system
Other concerns:
Pharmacokinetics
Pharmacodynamics
Clinical efficacy
Clinical safety
Pharmacovigilance system
Recommendations

4. New active substance status

VI. RECOMMENDED ADDITIONAL CONDITIONS FOR MARKETING AUTHORIZATION AND APPROVAL OF AN SMPC, PACKAGE LEAFLET (PIL)

1. Additional conditions for the Marketing Authorization
2. Approval of a version of the Summary of Product Characteristics (SmPC)
3. Labelling
4. Package leaflet (Patient Leaflet)
5. User consultation (see Section VII of this Report)

VII. QRD GUIDANCE AND CHECKLIST FOR THE REVIEW OF USER TESTING RESULTS

Product information

Name of the medicinal product	
Name and address of the applicant	
Name of the company which has performed the user consultation	
Type of Marketing Authorization application	
INN	
Pharmaco-therapeutic group (ATC Code)	
Therapeutic indications	
Orphan designation	□ Yes □ No
Assessor	

Full user consultation report submitted □ Yes □ No

□ Yes □ No

Summary report submitted

1. Grounds for bridging based on a sound justification:
   - □ extensions for the same route of administration
   - □ reference to test with same class of medicinal products
   - □ reference to test with same safety issues
   - □ other _____

Is the justification for bridging acceptable? (If no user testing report or summary report has been provided, a justification should be given) □ Yes □ No

Is the justification for not submitting a report acceptable? (e.g., administration in a hospital setting only, administration by a healthcare professional only, compliance with the QRD templates, long-established use of the product) □ Yes □ No

Grounds *[assessor's views on acceptability or not of the justification for not submitting user testing report or bridging form]*

1. Technical assessment

1.1. Recruitment

Is the interviewed population acceptable? □ Yes □ No

Comments/further details

1.2. Questionnaire

Is the number of questions _____ sufficient? □ Yes □ No

Questions cover significant (safety) issues for the PL concerned? □ Yes □ No

Comments/further details

1.3. Time aspects

Is the time given to answer acceptable? □ Yes □ No

Is the length of interview acceptable? □ Yes □ No

Comments/further details:

1.4. Procedural aspects

Rounds of testing including pilot

Comments/further details

1.5. Interview aspects

Was the interview conducted in well structured/organised manner? □ Yes □ No

Comments/further details

2. Evaluation of responses

2.1. Evaluation system

Is the qualitative evaluation of responses acceptable? □ Yes □ No

Does the evaluation methodology satisfy the minimum prerequisites? □ Yes □ No

Comments/further details

2.2. Question rating system

Is the quantitative evaluation of responses acceptable? □ Yes □ No

Comments/further details

3. Data processing

Are data well recorded and documented? □ Yes □ No

Comments/further details_____

4. Quality aspects

4.1. Evaluation of diagnostic questions

Does the methodology follow the Requirements for the medication guide (patient leaflet) and summary of product characteristics of medicinal products for human use subject to approval by the Eurasian Economic Commission? □ Yes □ No

Overall, each and every question meets criterion of 81% correct answers? □ Yes □ No

Comments/further details_____

4.2. Evaluation of the layout and design

Follows general design principles of the Requirements for the medication guide (patient leaflet) and summary of product characteristics of medicinal products for human use subject to approval by the Eurasian Economic Commission? □ Yes □ No

Language includes patient friendly descriptions □ Yes □ No

Layout navigable □ Yes □ No

Use of diagrams acceptable □ Yes □ No

Comments/further details_____

5. Diagnostic quality/evaluation

Have any weaknesses of the PL been identified? □ Yes □ No

Have these weaknesses been addressed in the appropriate way? □ Yes □ No

Comments/further details_____

6. Conclusion

Have the main objectives of the user testing been achieved? □ Yes □ No

Is the conclusion of applicant accurate? □ Yes □ No

Overall impression of methodology □ positive
□ negative

Overall impression of leaflet structure □ positive
□ negative

Conclusion/Overview _____

_____

APPENDIX 12
to the Rules of authorization
and assessment of medicinal products
for human use

TEST REPORT TEMPLATE

(template)

_____

(name of the competent authority of the Eurasian Economic Union Member State)

_____

(name of the expert organization or testing laboratory)

Accreditation certificate of the quality control laboratory _____

(number, expiration date)

_____

(address, telephone of the assessment organization (quality control laboratory))

TEST REPORT No. _____ dated DD.MM.YYYY

Applicant:	
Name and type of a material tested:	
Test type:	
Legal basis:	
Manufacturer, country:	
Batch, lot:	
Expiry date:	
Date of sample receipt:	
Number of samples provided:	
Start of the testing:	
End of the testing:	
Temperature and humidity:	
Material specification reference number:	

Testing results

Attribute name and analytical procedure code	Normative document acceptance criteria	Test results	Conclusion on compliance (complies or does not comply)

Conclusion

The samples provided comply (do not comply) with the normative document requirements.

Testing results do not comply with the requirements of normative document requirements in the following parameters:

1. ...

2. ...

Director of the Testing Center (Head of the Testing Laboratory)	_____	_____
	(signature)	(Full name)
Testing laboratory officer	_____	_____
	(signature)	(Full name)
	_____	_____
	(signature)	(Full name)
	_____	_____
	(signature)	(Full name)

Testing results apply to the samples tested only.

Full or partial reproduction of the Report without the permission of the testing laboratory (center) is prohibited.

_____

APPENDIX 13
to the Rules of authorization
and assessment of medicinal products
for human use

GUIDANCE DOCUMENT
on the content of the critical assessment report on non-clinical aspects

I. GENERAL GUIDANCE

The assessment report on non-clinical aspects (hereinafter referred to as the report) should be sufficiently detailed to allow for secondary assessment by other assessors of the competent authorities or organizations of the Member States of the Eurasian Economic Union.

The report should describe salient findings and especially those deficiencies that justify the questions intended for the applicant. These questions will also be listed in the overview assessment report on safety, quality, and efficacy.

Cross-references should be used to clearly indicate the origin of any information used in the report, such as the specific parts of the dossier (e.g. overview, summary, study reports), references to the literature or other sources.

Critical assessment (e.g. comments on the validity and interpretation of the data, conclusions) should be described in the "Assessor's comments" sub-sections that follow each chapter. The words 'Major Objection – see proposed List of Questions' may be used when necessary.

The report should indicate whether findings have implications for human safety and whether additional expertise is needed to assess this (e.g. there are findings regarding carcinogenicity but receptors are different between target species and man).

The report should also emphasize findings that need to be reflected in the SPC.

Reference to information which is confidential and should not be seen by the applicant (e.g. reference to the assessment of another medicinal product) should be clearly marked as "Confidential" and highlighted using a yellow background. These sections will be removed before the assessment is sent to the applicant.

The use of tables/graphs/figures is encouraged; examples are given in the template as laid down in Appendix 6 to the Rules of authorization and assessment of medicinal products for human use (hereinafter referred to as the Authorization rules) and are to be used as appropriate. PK/TK tables should include the number of animals and standard deviation for each parameter. For repeat-dose studies, TK day of sampling should be mentioned. Tables taken from the dossier may also be included into the assessment. Put appropriate footnotes.

Separate pages have been added in the template as laid down in Appendix 6 to the Authorization rules for the inclusion of a list of abbreviations and a list of references, to be completed when necessary.

It is recommended that the font used in the main text be Times New Roman, size 11. Where there are more than 7 pages in the report, Table on Contents shall be envisaged.

When drawing up the report the assessor may refer to the Common Technical Document guidance texts of the Union.

This guidance contains only those sections where clarification or explanation is needed.

II. NON-CLINICAL CRITICAL ASSESSMENT

1. Introduction

1.1. Type of application and aspects on development

Type of application

Indicate type of marketing authorization application (reference to the legal basis of the application), e.g. complete independent application, mixed application, well established use application, biosimilar application etc., and if acceptable justifications exist for waiving certain studies or replacing original studies by literature data. If certain studies are only available as publications it is important to clarify whether or not such studies are/are not of sufficient quality to allow an in depth assessment of crucial data.

For each main section of the assessment report for modules 4 and 5, the report should describe the data submitted in accordance with the requirement of Appendix 1 to Authorization rules. The types of studies addressed within each section should include all indents as listed in Annex I. For each type of study, after distinguishing between main and supportive data, it should be assessed whether the main data consist of all the particulars and documents of clinical study reports ("original data"), bibliographical references, a combination of the two, or if data are absent.

The data submitted should be assessed based on the legal basis of the application, other legal/regulatory data requirements, applicable guidelines and other scientific criteria.

Where the data submitted deviate from the requirements, the acceptability of any justifications should be assessed. In particular, absence of any data for non-clinical/clinical test or trials, or use of bibliographic references substituting in part or completely original data for main studies must be justified.

If data from publications is used by the applicant or in the context of the assessment, a clear referencing should be included allowing for clear identification of the publications. Consider generation of a reference list if a substantial number of publications is used. If appropriate ensure clear expression of the view on the content of a publication (e.g. if used not only as data reference but in the context of a discussion).

Examples of justifications and assessment of the justifications are provided in the following table.

Justification	Assessment
Specific derogations foreseen in Appendix 1 to Rules of authorization and assessment of medicinal products for human use	Mention specific derogations and confirm the reasons why the application fulfils the conditions for applying them.
Specific derogations foreseen in guidelines, with particular reference to Union or Member State guidelines	Mention guidelines and specific derogations, and give reasons why the application fulfils the conditions for applying them.
Due to the extent of scientific knowledge the conduct of certain clinical trials is considered unethical (in accordance with the Rules on the Good Clinical Practice of the Eurasian Economic Union subject to approval by the Eurasian	Discuss what evidence is the basis for the scientific knowledge, the relevance and reliability of such evidence, and assess the validity of any extrapolation. Discuss any deviations from conventional

Economic Commission, Member State legislation on animal protection), or the conduct of certain animal tests is considered to lead to unnecessary use of animals (for instance, due to extensive clinical experience certain toxicological tests are considered unnecessary) Given that evidence, assess whether repeating certain trials/tests (or conducting additional tests) would extend scientific knowledge essential for benefit/risk assessment and provision of adequate information to patients and prescribers.	development plans, particularly about the timing of animal tests and the conduct of clinical trials, as described in the legislation and applicable guidelines, and any impact on the final risk-benefit assessment.
The applicant is unable to provide comprehensive data on the efficacy and safety of the product under normal conditions of use ("exceptional circumstances" or conditional approval")	For exceptional circumstances, the assessor should assess the validity of the reason(s) following those listed in section Imposing of post-marketing measures (conditional marketing authorization) of the Authorization rules for granting a conditional marketing authorization subject to annual renewal. Note that conditional approval will normally not include specific obligation on the non-clinical part – exceptions are "emergency situations"

Aspects of development.

Introduce and comment the non-clinical development programmer in view of the proposed indication and posologies (indicate if there is a paediatric indication or development). State if the range of studies is in agreement with Union guidelines or Member State legislation.

Indicate if the applicant has requested accelerated assessment and the fulfilment of relevant criteria.

In the particular case of a "bio-comparability exercise", the development strategy chosen by the company should be described, justified and assessed in view of the relevant guidelines. For similar biological medicinal products the relevant legal acts which constitute the Union law have to be taken into consideration. An extensive comparability exercise will be required to demonstrate that the similar biological and reference products already authorized in the community have similar profiles in terms of quality, safety and efficacy. Detailed information of the reference product (name) strength, pharmaceutical form, MAH, date of authorization in the Union and the detailed information (such as batch number and country of origin) of the batches used in the comparability exercise (quality, non-clinical and clinical): need to be provided in tabular format in the quality part of this report.

Indicate whether a Paediatric Investigation Plan (with or without deferral) or a product-specific waiver has been agreed with the competent authorities and organizations, or whether a class waiver applies. Briefly summarize the conditions and principal requirements of the paediatric investigation plan with regard to nonclinical aspects, if applicable, and state the relevant key information about the current status of the nonclinical studies (i.e. completed, studies ongoing, etc).

State if, and when Scientific Advice/Protocol Assistance has been given, describe the issues and indicate whether the advice followed by the applicant.

Indicate if, and when Orphan Drug designation has been granted. If relevant, indicate any potential similarity issues concerning mechanism of action.

In cases where batches other than the one intended for marketing was used in part of the studies, a qualification of new impurities (if any) should be assessed.

1.2. Good Laboratory Practice aspects

Statements on compliance with the Rules of the Good Laboratory Practice of the Union subject to approval by the Eurasian Economic Commission (hereinafter referred to as GLP) shall be addressed here and also in the overview assessment report on safety, quality, and efficacy.

In this section specifically address:

- Any concerns raised during the assessment about compliance with GLP requirements (data accuracy or protocol compliance).
- Discuss the need for a GLP inspection.
- To request a GLP inspection:
- Contact the Member State pharmaceutical inspectorate;
- Determine with an inspector the studies, sites and special concerns or issues related to the inspection.
- Formulate the formal inspection request for review by the inspectors and agreement by the competent assessment organizations of the Member States for adoption by the competent authorities of the Member States and inclusion in the inspection plan (day 90 or 120 of the granting a marketing authorization).

2. Pharmacology (MODULES 2.6.2 AND 4.2.1)

Brief summary

Active substance, mode of action and brief rationale for the development of the product in the proposed indication should be described.

For similar biological medicinal products this section should highlight the comparative nature of the studies and rational for the non-clinical development program. (The discussion of the results can come under point “discussion” at the end of the section.)

Physical chemistry

The table template shall be completed in accordance with Appendix 8 to the Authorization rules. If it is impossible to complete any cells of the table, an appropriate statement shall be made and the significance of the missing information shall be assessed.

2.1. Primary pharmacodynamics

This section should address PD studies in relation to the disease to be treated and the proposed indications including the following points:

- Proof of concept (in-vitro and in-vivo) and mode of action.
- Availability of animal models relevant for the proposed indication/ interspecies comparison.
- Activity (e.g. ED50) including the species used in toxicology studies.
- Preliminary PK (plasma concentration) in animal models if available.
- Duration/reversibility of effects, resistance profiles (anti-infectives).
- Pharmacologically active metabolites (relative contribution to pharmacodynamics).
- Immunological properties, including antigenic specificity for monoclonal antibodies.

For antimicrobial medicinal products the mechanism of action, in vitro spectrum of activity including wild type distribution of MIC values (if available), post antibiotic effects and mechanism of resistance should be described. The in vivo efficacy in animal model by species of bacterium for example should be described.

The PK/PD relationship established in animal model could be described here or under pharmacokinetics. The clinical section should cross-refer to this information.

For similar biological medicinal products:

A battery of receptor-binding studies or cell-based assays, (many of which may already be available from quality-related bioassays), are normally a part of the comparability exercise in order to assess if any differences in reactivity are present and to determine the likely causative factor.

Animal studies are designed to maximize the information obtained and to compare reference and similar biological medicinal products intended to be used in the clinical trials. Such studies are performed in a species known to be relevant and employ state of the art technology.

2.2. Secondary pharmacodynamics

This section should describe pharmacological effects other than the primary therapeutic activity (previously general pharmacology). Mention receptor screen(s) as appropriate.

For monoclonal antibodies, the immunological properties of the antibody other than those intended should be described here in detail, including complement binding and any unintentional reactivity and/or cytotoxicity towards human tissues distinct from the intended target. Such cross- reactivity studies can be carried out using a range of human tissues and should be described.

2.3. Safety pharmacology

The following points should be addressed:
a) Core battery (GLP):

- Cardiovascular system (including QT prolongation in-vitro/in- vivo)
- Central nervous system
- Respiratory system

b) Other e.g. Renal and GI system
For similar biological medicinal products normally other routine toxicological studies such, as safety pharmacology studies are not required for similar biological medicinal products, unless indicated of results of repeat dose studies

2.4. Pharmacodynamic drug interactions
Potential pharmacodynamic drug interactions may include:

- Interactions at receptor level
- Possible co-medications in the clinical setting
- Alerts from safety pharmacology, PK/metabolism or toxicology studies

2.5. Assessor’s overall conclusions on pharmacology

The content of this paragraph could be carried forward to the overview assessment report on safety, quality, and efficacy of the assessment.

A self-standing and focused elaboration might therefore be necessary to allow the reader comprehensive access to the relevant findings.

summarize the salient results from the main pharmacology studies and discuss the relevance of the models used for the intended therapeutic indication.

Provide an overview of the salient secondary and safety pharmacology findings, emphasizing those predicting potential adverse events in humans.

As an alternative, this section could simply state the main conclusions, in which case the text in the overview assessment report on safety, quality, and efficacy should be elaborated on separately.

Highlight any areas of agreement / disagreement with the "non- clinical overview" in the submitted dossier and comment on the suitability of the SPC wording. Ensure correspondence with SPC (particularly 5.3 Preclinical safety data but also e.g., sections 4.3, contraindications,4.5 Interactions, 4.6 Pregnancy and lactation, 5.1 Pharmacodynamic properties, if relevant) and that all information in the SPC is explicitly assessed and supported by the scientific assessment.

3. Pharmacokinetics (MODULES 2.6.4 AND 4.2.2)

Pharmacokinetic studies

Brief overview of studies. See further toxicokinetic studies in repeat-dose toxicity.

3.1. Methods of analysis

The assessment report should contain a brief discussion on the methods of analysis and their validation. When used in toxicokinetic studies they should comply with GLP.

Units of measurement should be clearly defined (e.g. molarity or mg/ml) and the same units used consistently as much as possible.

The assessor should comment on the availability of this information and on any discrepancies between the studies.

3.2. Absorption

- Points of discussion may include:
- Site of absorption for oral preparations if possible (usually not known which GI segment(s) involved)
- Single and repeat dose kinetics
- Dose proportionality
- Gender differences if available
- Interspecies comparison (species used in toxicology studies and data in humans should be included)
- Absolute bioavailability
- Formation of neutralizing antibodies (biotech products).

Tabulation of the data may be a useful aid, including e.g. species, dose, route, C_{max}, t_{max}, AUC, $t½$, V_d, Cl_t and F% (see example below).

Where the PK is linear, representative data are sufficient. Examples of tables to tabulate absorption data:

3.3. Distribution

The following data should be considered:

- Tissue distribution studies mention of method (e.g. autoradiography).
- Protein binding (albumin, other) in different species with estimation of the free fraction including humans.
- Distribution in blood cells if possible (not systematically done).
- Placental transfer studies.
- Melanin binding (specific study in pigmented rat!).
- Excretion in the milk should be highlighted.

Discuss degree of distribution in relation to possible target organs for toxicity and tissue retention if applicable (especially if effects at site of retention).

Plasma protein binding should be considered. Data in humans should be included and interspecies comparison made. The need to compare free concentrations should be addressed.

If there are indications of melanin binding, the need for assessment of phototoxicity should be commented, considering e.g. degree of light absorption; possible DNA binding should be also considered.

Distribution of parent compounds vs metabolites to be discussed in this context as appropriate.

3.4. Metabolism

The following data should be considered under the following headings:

- Chemical structures and quantities of metabolites in biological matrices (table).
- Possible metabolic pathways (add picture if available).
- Presystemic metabolism (GI/hepatic first-pass effects).
- In vitro metabolism, mainly P450 (microsomal) studies: affinity, substrate specificity for subfamilies, inhibition studies (if positive, type of inhibition: reversible, suicide), drug interactions (clinically relevant associations). Non-microsomal oxidations, reduction, hydrolysis if applicable.
- Enzyme induction.
- Phase II (conjugation) metabolism mainly in-vivo.

It is important to compare metabolic patterns in animals and humans.

Identify if there are species-specific metabolites, particularly if the animals used for safety testing do not form metabolites that have been identified in humans.

This is an important part of the assessment of the relevance of the animal models used.

3.5. Excretion

It may be useful to tabulate data (see example below). Comment on routes of excretion which could be of value for assessment of organ specific toxicity.

If there are major differences in excretion patterns (metabolites) between animal and human, the animal species may be of less relevance to assess toxicity related to respective excretion organ.

Data and comments on mass balance should be included.

3.6. Pharmacokinetic drug interactions

Focus on interactions with drugs that are potentially going to be co-administered in the clinical situation.

3.7. Other pharmacokinetic studies

If relevant, use the following headings:

- Studies in juvenile animals
- Studies in pregnant animals
- Studies in animal models of disease

3.8. Assessor’s overall conclusions on pharmacokinetics

The content of this paragraph could be carried forward to the overview assessment report on safety, quality, and efficacy of the assessment.

A self-standing and focused elaboration might therefore be necessary to allow the reader a comprehensive access to the relevant findings thus enabling adequate benefit risk assessment

Give an overview of the salient pharmacokinetic features. Comment on the relevance of the animal species used in the toxicity testing for human safety assessment e.g. considering metabolic patterns. Other important aspects may include major differences in

absorption/bioavailability, interindividual/interspecies variability, elimination rates (differences in t½), etc.

Comment on other issues that may be of importance for the safety assessment e.g. distribution to target organs, excretion routes, and pharmacologically active metabolites. Discuss interspecies differences and compare with the clinical situation.

As an alternative this section could simply state the main conclusions in which case the text in the overview assessment report on safety, quality, and efficacy should be elaborated on separately.

Ensure correspondence with SPC (particularly 5.3 Preclinical safety data but also e.g., sections 5.2 Pharmacokinetic properties, 4.3 contraindications, 4.5 Interactions, 4.6 Pregnancy and lactation, if relevant) and that all information in the SPC is explicitly assessed and supported by the scientific assessment.

4. Toxicology (MODULES 2.6.6 AND 4.3.3)

4.1. Single dose toxicity

The duration of observation (14 days in a standard GLP study) and a short statement on whether studies revealed low or high acute toxicity should be included.

It is considered useful to include the approximate lethal dose or observed maximum non-lethal dose.

The clinical signs of acute toxicity (briefly) and the mode and time of death (early/same day or delayed).

Target organs, (histo)pathology if available.

4.2. Repeat-dose toxicity

The pivotal studies should be organized by species and route of administration. Comment on GLP for overall programmer and specify any deviations (e.g. contamination of controls).

A short description of the design (strain, route of administration, dose groups, number animals/gender/group, recovery groups if any, TK if performed).

The main findings should be comprehensively described, namely; death, body weight, relevant laboratory findings, target organs with type of histopathological lesions, dose-dependency, onset, severity, species or gender related differences and duration of toxic effect.

The No Observed Adverse Effect Level (NOAEL) in the different species should be provided (if established) with comments on the relation of the systemic exposure at that dose level to the systemic exposure in humans given the maximum intended dose (exposure margin).

A statement whether reversibility has been demonstrated in the recovery group should be included.

Comments on TK (linearity, gender dependency, accumulation).

The use of tables (example below) or figures could facilitate the comprehension of the largely descriptive tests.

Highlight the important findings; discuss the mechanistic background and the margin to the clinical exposure.

For similar biological medicinal products usually at least one repeat dose toxicity study, including toxicokinetic measurements has been conducted. Toxicokinetic measurements including determination of antibody titers, and cross reactivity and neutralizing capacity are part of this study. The studies allow detection of relevant differences in toxicity and/or immune responses between similar biological medicinal product and reference product.

Normally other routine toxicological studies such reproduction toxicology, mutagenicity and carcinogenicity studies are not required for similar biological medicinal products, unless indicated from results of repeat dose studies.

Toxicokinetics

Analyses of plasma samples from control animals should be included. Example of a table to show toxicokinetic studies:

4.3. Genotoxicity

Provide an overview of the tests performed.

Sort the performed tests according to the 'level' of genotoxicity, i.e. mutagenicity (gene mutations), chromosomal aberrations (clastogenicity) in-vitro, chromosomal aberrations (clastogenicity) in- vivo, primary DNA damage and other genotoxic effects.

Preferably, present results in a table (see example table of the similar section in Appendix 6 to Authorization rules) and add comments if needed in the text below.

If there are no remarkable findings in the in-vitro tests, inclusion in the table is sufficient.

The relevance of the species used in the in-vivo tests as well as of the system used for metabolic activation (e.g. S9 fraction) in the in- vitro tests, based on comparisons with the metabolic pattern in humans should be commented on.

A statement on the exposure should always be included for the in-vivo tests (refer to toxicokinetics studies).

Issues to consider when evaluating genotoxicity tests:

a) For in-vitro tests:

- Which strains /cells are used and which endpoints.
- Selection of concentrations.
- Stability in the medium (check of concentration/degradation products).
- Metabolizing system.
- Positive and negative controls.
- Treatment time/sampling time.
- Criteria for positive response.
- Concentration-response relationship.
- Reproducibility.
- Cytotoxicity / cell survival.

b) For in-vivo tests:

- Which species/strain/model was used?
- Number and gender of animals.
- Doses and exposure.
- Exposure established by toxicity or kinetics.
- Metabolic differences between species and human.
- Treatment and sampling times.
- Applicant's criteria for positive response.
- Dose/time-response relationship.

Example of a statement that can be used when summarizing the genotoxicity test battery:

The genotoxicity of X has been studied with respect to gene mutations in bacteria and mammalian cells and chromosomal aberrations in-vitro and in-vivo. Additionally, tests of primary DNA damage in-vitro and malignant cell transformation have been conducted.

Issues to discuss:

- Positive findings in either in-vitro or in-vivo tests.
- Mechanistic background: mutagenic or clastogenic.
- Is a threshold approach possible?
- Conclusions on the genotoxic potential.

4.4. Carcinogenicity

4.4.1. Long-term studies

Give a short presentation of the studies that have been performed, preferably as a table under respective subheading, e.g. long-term studies; short-term, other etc. (example below).

If carcinogenicity studies have not been performed the applicants' justification should be discussed.

Give a short summary of results including neoplastic changes as well as relevant non-neoplastic changes, as appropriate. Non-neoplastic changes should be discussed with reference to the observations in repeat-dose toxicity studies. Preferably, list results in a Table (see example table of the similar section in Appendix 6 to Authorization rules).

Issues to be considered in detail:

- Species strain and gender.
- Number of groups (control groups).
- Number of animals per group.
- Route of administration
- Duration of treatment.
- Growth (BW gain and FC)
- Survival at the end of the study.
- Toxicokinetics (in a table: day of sampling, AUC,). Sampling of controls
- Tumour findings organs, type (B or Malignant), incidence.
- Pre-neoplastic findings.
- Nomenclature of tumors.
- Statistical methods used.
- Toxic findings not seen in the studies of shorter duration.

4.4.2. Short or medium-term studies

New models:

- Which models and the rationale for use.
- If genotoxicity under discussion.
- Number of animals and treatment period.
- Use of positive control and the response.
- Use of comparative compound (if applicable).
- Statistical analysis of most important tumors.

4.4.3. Other studies

If present, e.g. mechanistic studies to explain a tumorigenic effect of the product or metabolite(s).

4.5. Reproductive and developmental toxicity

Give a summary presentation of the performed studies, preferably in a table (example below) including dose-finding studies, as appropriate.

Comment on GLP for each pivotal study. If the information contained in the table is not sufficient for a particular study, factual data may be further described under each specific heading below.

Consider information relevant to reproduction toxicity from other sections of the dossier, either as cross-reference or facts. For instance, histopathology of reproductive organs from repeat-dose toxicity, endocrine effects, pharmacokinetics, pharmacodynamics should be considered.

4.5.4. Studies in which the offspring (juvenile animals) are dosed and/or further evaluated

Conclusions on the reproductive toxicity.

Comment on the relevance of the tested systems used (e.g. species/strain) (e.g. based on comparative metabolism and kinetics, comparative pharmacodynamics).

Evaluate exposure and distribution data in pregnant and/or lactating animals, and in offspring (including milk excretion).

Include critical assessment on each specific area of the studies and provide concluding remarks considering relevant findings.

Consider margins of exposure and assess the clinical relevance of the findings.

Provide suggestions and justifications for SPC recommendations.

4.6. Local tolerance

A short comment on whether the compound showed any evidence of local irritancy at the site of administration. Sensitization studies (see 4.7.1, should be included if applicable (dermal route).

4.7. Other toxicity studies

Any such studies should be noted and findings commented upon.

4.7.1. Antigenicity

Antibody formation, sensitization (guinea pig assay) where applicable.

4.7.2. Immunotoxicity

When performed, specific immunotoxicity investigations (together with relevant findings in repeat dose toxicity) should rather be discussed here especially when clinical implications are suspected.

Such studies may include cell surface markers (immuno-histology or flow cytometry), functional tests (primary Ab formation to SRBC, NK activity, macrophagic function, delayed hypersensitivity, host resistance tests, complement activation etc…).

See also guidance on repeat dose toxicity.

Implications for immune suppression, autoimmune potential, hypersensitivity reactions, in humans, should be mentioned.

4.7.3. Dependence

In conjunction with pharmacodynamic studies/models (not done routinely in toxicology).

4.7.4. Metabolites

Specific studies for major human metabolites (or isomers) insufficiently present in animals.

4.7.5. Studies on impurities

Studies for qualification of impurities: single or repeat dose, genotoxicity, reproduction. See ICH guidelines

4.7.6. Other studies

If appropriate, e.g.: Phototoxicity

Includes dermal/ocular photoxicity (when relevant), photosensitisation, photo-genotoxicity and photo-carcinogenicity. Possible need of such studies depends on photo-absorption/degradation, dermal/ocular use/exposure (see relevant guidance).

Molecular toxicology

Reactive metabolites (in-vitro covalent binding to proteins, lipids, nucleic acids). Possible implications for idiosyncratic reactions or autoimmune diseases.

Other mechanistic studies (mitochondrial toxicity, Hb reactivity etc…)

Other mechanistic studies (mitochondrial toxicity, Hb reactivity etc…), -omics data

4.8. Ecotoxicity/environmental risk assessment

The content of this paragraph could be carried forward to the overview assessment report on safety, quality, and efficacy of the assessment.

A self-standing and focused elaboration might therefore be necessary to allow the reader a comprehensive access to the relevant findings thus enabling adequate benefit risk assessment.

Any deviations from the toxicology program as stated in the guidelines or from GLP or any absence of required studies should be commented upon.

If it is a bibliographical application or if bibliographical data are used as supportive information, it is particularly important to highlight this.

In general, the rationale for the selection of species/systems, duration and dose/concentrations used in the studies should be provided.

Explanations for the observed effects as well as statements pertaining to the potential relevance for the human use as suggested by the applicant should be commented and if possible concluded upon.

The implications of any differences in the chirality, chemical form, and impurity profile between the compound used in the non-clinical studies and the product to be marketed should be discussed.

Interspecies comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, Cmax, and other appropriate parameters) should be discussed and the limitations and utility of the non-clinical studies for prediction of potential adverse effects in humans highlighted.

The relevance of the animals in toxicity studies should also be discussed with respect to potential interspecies differences in pharmacology.

Special emphasis should be put on genotoxicity, carcinogenicity and reproductive and developmental toxicity findings. In case of positive genotoxic effects, tumor findings and/or developmental/reproductive toxicity findings, the possible relevance for the human situation should be discussed and if possible concluded upon.

For the carcinogenicity potential consider:

Biological significance of tumor increases, historical data, relation to pharmacological effect, dose-related effects, species-specific differences, mechanistic studies, relationship with genotoxicity and comparison between human and animal exposure etc.

As an alternative this section could simply state the main conclusions in which case the text in the overview assessment report on safety, quality, and efficacy should be elaborated on separately.

Please indicate if additional expertise is needed to assess the human implications. This includes whether there is a need to obtain an Opinion from the competent authority related to data with relevance to the paediatric development.

Comment on the suitability of the SPC wording. Ensure correspondence with SPC (particularly 5.3 Preclinical safety data but also e.g., sections 4.3 contraindications, 4.5 Interactions, 4.6 Pregnancy and lactation, if relevant) and that all information in the SPC is explicitly assessed and supported by the scientific assessment.

For similar biological medicinal products the similarity / differences in response between the similar biological product and the reference product and not just the response per se is discussed.

6. List of questions proposed by the assessor

"Major objections", preclude a recommendation for marketing authorization. In principle, one major objection may entail more than one question and the use of bullet points or subheadings is encouraged. It is vital that the structure and content of a major objection are clear and understandable to the reader. Detailed comments may be necessary along with a reference to guidance documents.

Ideally, the objection should include a clarification as to what kind of response/action is expected from the applicant.

"Other concerns", may affect the proposed conditions for marketing authorization and product information. Other concerns should be resolved before approval; failure to do so may render the application un-approvable.

This list should be carried forward to the overview assessment report on safety, quality, and efficacy.

'Recommendations' shall contain assessor's comments/conditions which do not preclude granting a marketing authorization and which might be resolved having the marketing authorization been granted using variation to a MAA procedure.

7. Recommended conditions for marketing authorization and product information

Points relating to this heading should also be specifically addressed in the relevant section of the overview assessment report on safety, quality, and efficacy, (e.g. specific comments on the product information).

More general comments could also be made here.

APPENDIX 14
to the Rules of authorization
and assessment of medicinal products
for human use

GUIDANCE DOCUMENT
on the content of the critical assessment report on quality aspects

I. GENERAL GUIDANCE

This guidance contains only those sections where clarification or explanation is needed.

In general, the following aspects should be considered:

The report should be sufficiently detailed to allow for secondary assessment by other assessors of the competent authorities or organizations of the Member States of the Eurasian Economic Union (hereinafter referred to as Member States and Union, respectively).

The report should describe salient findings and those deficiencies that justify the questions intended for the applicant. These questions will be listed in the overview assessment report on safety, quality, and efficacy.

Cross-references should be used to clearly indicate the origin of any information used in the report, such as the specific parts of the dossier (e.g. overview, summary, study reports), references to the literature or other sources.

The report should also emphasize those findings that need to be reflected in the SPC.

The use of tables/graphs/figures is encouraged; examples are given in the template as laid down in Appendix 8 to the Rules of authorization and assessment of medicinal products for human use subject to approval by the Eurasian Economic Commission and are to be used as appropriate. Tables taken from the dossier may also be included into the report. Put appropriate footnotes. Applicant's data such as flowcharts, specifications, etc. can be included in the report to facilitate assessment.

Separate pages have been added in the template as laid down in Appendix 8 to the Rules of authorization and assessment of medicinal products for human use subject to approval by the Eurasian Economic Commission for the inclusion of a list of abbreviations and a list of references, to be completed when necessary.

It is recommended that the font used in the main text be Times New Roman, size 11. Where there are more than 7 pages in the report, Table on Contents shall be envisaged.

II. QUALITY CRITICAL ASSESSMENT

The following structure for the quality assessment report keeps basically to the CTD structure of the dossier, apart from some preliminary sections, e.g. an Introduction section to put the product in context.

Whilst this guidance is relevant for both NCE, known chemical active substances and Biotech/Biological products, in some cases specific additional guidance is given for either NCE or Biotech/Biological products.

Please also refer to the CTD guidance text for the applicant – it is not considered necessary to repeat this here, but rather to highlight some additional aspects not specifically detailed in the

CTD, for the benefit of assessors. Note that for simplicity, not all CTD headings are reproduced in the report structure that follows, only the 'main' headings. Assessors may add more, or less, depending upon the complexity of the product.

Reference to information, which is confidential and should not be seen by the applicant (e.g. reference to the assessment of another medicinal product) should be clearly marked as "Confidential" and highlighted using a yellow background. These sections will be removed before the assessment is sent to the applicant.

This quality assessment report should be 'self-standing'. This may be achieved in two ways:

1) Presenting or copying data which are taken from the applicant's dossier, followed by the assessor's own critical assessment of these data, particularly with respect to safety/efficacy consequences and highlighting adherence to specific guidance documents. The heading 'Assessor's Comments' should be introduced as a separator in this case, to avoid confusion.

2) Alternatively, this report may consist largely* of the assessor's own views with references to the applicant's own data and/or Quality Overall Summary (QOS). In this case, the assessor's views are intended to be read in conjunction with the QOS which must be attached. The additional headings for assessor's comments would not be needed.

An assessor may also use relevant guidelines and guidance when drawing up the report.

In general, assessors should try to relate quality matters to efficacy and safety consequences as much as possible. Matters arising from the scientific evaluation below, which have a bearing on the product information, should also be mentioned (comments on the SPC, Labels & Package Leaflet.).

In the case of an application for a similar biological medicinal product an extensive comparability exercise will be required to demonstrate that the similar biological and reference products already authorized in the Union have similar profiles in terms of quality, safety and efficacy.

Detailed information of the reference product (name) strength, pharmaceutical form, MAH, date of authorization will be checked during validation. In addition to these details the batch number and country of origin of the batches used in the comparability exercise (quality, non-clinical and clinical) should be confirmed by the assessor and need to be provided in tabular format in the quality part (Product: Reference Standards or Materials, Appendix 4 to the Rules of authorization and assessment of medicinal products for human use subject to approval by the Eurasian Economic Commission, CTD Module 3.2.P.6).

For similar biological medicinal products the relevant guidelines of the Union and Member States should be taken into consideration. Other guidance for biotechnology derived medicinal products in general is also applicable.

The quality comparability exercise for a similar biological medicinal product is an additional element to the CTD dossier. Applicants should provide distinct sections where appropriate on these comparisons for ease of assessment and this should be done on the basis of concluding in a concise summary in the overview assessment report on safety, quality, and efficacy as to whether comparability has been demonstrated for both the active substance and finished product.

1. Request for inspection action of pharmaceutical manufacturing prior to authorization

Where a site has already been inspected, such requests are expected to be uncommon. However, when quality issues requiring a future inspection are identified during the dossier

assessment phase, they should be notified as soon as possible to the relevant Inspections authority.

Because an inspection takes time to organize, this action shall be taken prior to authorization.

The relevant authority should be notified; if possible, in advance of the assessment report drawn up, and this request should be highlighted in this part of the assessment report.

Of note, request might be initiated based on the evaluation of any modules concerning quality aspects.

It is important to note that such requests may be made to resolve questions in any part of the quality dossier, and the reasons for the request should be briefly described here and in more detail in the relevant section of the report which follows, e.g. S.2, P.3, etc., for either GMP-compliance and/or product-process specific inspections:

Active substance manufacturing site:

In the manufacture of medicinal products, active substances which have been manufactured according to the Rules on the Good Manufacturing Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission.

It is the responsibility of the manufacturing authorization holders using the active substance as a starting material to ensure the GMP compliance of their suppliers of active substances.

However, inspections may be requested on when there are causes for concern raised during the assessment for any site.

It should be particularly noted that inspections should be triggered automatically in the case of a biological substance or for the sterilization step of a sterile active substance when there is no evidence that the site in question is subject to routine inspection by a Competent Authority.

Finished product manufacturing site

The manufacturing site is a medicinal product manufacturer’s territorially separate facility the designed to perform the complete manufacturing process of medicinal products or any step thereof including intermediate step and quality control.

An inspection may always be requested to cover product or process specific issues. In which case, a list of questions/items should be provided to the inspectorate, which should be addressed during the inspection.

Testing

An assessor shall define the testing protocol (type of samples: active, bulk, finished product / tests to be carried out / number of samples / number of batches / testing laboratory) where laboratory testing is indicated in accordance with Rules of authorization and assessment of medicinal products for human use the Eurasian Economic Union subject to approval by the Eurasian Economic Commission.

2. Introduction

General background of the medicinal product

General background of the product shall include the following:

- Brief description of the product type (active substance {e.g. NCE, known chemical active substances, Biotech/Biological) radiopharmaceutical, herbal}, pharmaceutical form, container). Highlight if a paediatric formulation was developed.
- Orphan Medicinal Product (OMP) status, if relevant.

- Indications, target population, posology (with regard to the ability of the product to deliver this posology, e.g. scored tablets), method of administration (if unusual, e.g. using a device).
- Mention relationship of active substance to others in the same therapeutic class.
- Preparation/reconstitution of product (e.g. radiopharmaceuticals, lyophilizate).
- Other special features of the product such as delivery or administration systems, medical devices etc.
- Linked or related applications (e.g. drug of a pro-drug, line-extension, simultaneous or 'double' applications).

The information provided here is intended to provide a brief description of the main critical features of the product. The amount of information provided will depend on the nature of the particular product. The clinical context of use should also be briefly mentioned.

Name:

Dosage form and strength:

Procedure:

Therapeutic class or indication:

Proposed dosage range:

3. Active substance (CTD module 3.2.S)

Note that if information on the active substance is presented in the form of an Active Substance Master File (ASMF) with a confidential/closed part this should be stated here. The assessment of this closed or restricted part dealing with information which is protected by intellectual property rights or which is otherwise sensitive should be done in a separate report, together with a separate list of questions arising from this report, attached as an Annex (see Appendix 8 to the Rules of authorization and assessment of medicinal products for human use subject to approval by the Eurasian Economic Commission). Note ASMFs are not applicable for biological medicinal products.

3.1. General information (CTD module 3.2.S.1)

Under this heading, the following CTD Headings would be discussed:

S.1.1 Nomenclature

Chemical name shall be provided, where appropriate. whether the name is rINN, pINN, Common Name, etc.

S.1.2 Structure

Structure: Include this and link to similar compounds, by description or by structure.

S.1.3 General Properties

General properties: Also specify the properties relevant to the performance of the product in the clinic and give values, e.g., pKa, solubility, polymorphism, isomers, particle size distribution etc. where relevant.

For biotech/ biological substances, S.1 should also include a description of the active substance. The name and description of the molecule should be given. This should include features such as glycosylation/post-translational modifications, "artificial" modifications (amino-acid substitutions, pegylation.), molecular size. Information on secondary and tertiary structure should be given if appropriate. Highlight and discuss elements of structure important for mechanism of action.

Identify those issues not adequately covered and which need to be addressed in the LoQ (with reference to question number, if wanted). Identify 'Major' issues.

NOTES: 1. It should be mentioned whether a CEP or ASMF procedure or full information in the dossier of the AS in the dossier is used.

2. In case the ASMF procedure is used it should be mentioned that the assessment of the Active Substance Master File (ASMF) is provided in a separate ASMF Assessment Report with a confidential annex on the Restricted Part.

3. Where there is more than one ASMF cited in the dossier, a separate report is provided for each ASMF

4. Letters of Access in relation to specific medicinal products should be described for the product in question.

5. When a CEP or ASMF is used, only section 3.4 Control of Active Substance and 3.5 Reference Standards or Materials relating to the product manufacturer need completing, unless the applicant has provided additional data e.g. 3.2.S.7 stability data to support a longer re-test period.

6. The questions to the restricted part of the ASMF reports will not be sent to the MAH but only to the relevant ASM/holder of the ASMF

7. Where ASMF or CEP is applicable, clarify the source (applicant or ASMF holder or CEP holder) and level of details to be drafted in the assessment report.

8. The assessment of the active substance in this AR should only address additional information provided by the applicant, which is not included in the open part as provided by the ASMF holder. In case a full dossier for the Active Substance is provided by the applicant the full assessment of the active substance should be included in the AR.

Nomenclature (CTD section S.1.1)

International non-proprietary name (INN):

United States Adopted Name (USAN):

Chemical name, where appropriate:

Other name:

CAS registry number:

Laboratory code:

Molecular formula:

Relative molecular mass:

Structure (CTD module S.1.2)
General Properties (CTD module S.1.3)

Physical characteristics:
Solubility:
pKa-value:
Solution pH (where possible)
Melting point (for solids)
Partition coefficient:
Hygroscopicity:
Stereochemistry:
Polymorphism:
Degree of crystallinity (for solids)

3.2. Manufacture (CTD module 3.2.S.2)

Under this heading, the following headings would be discussed:

S.2.1 Manufacturer(s)

S.2.2 Description of Manufacturing Process and Process Controls

S.2.3 Control of Materials

S.2.4 Controls of Critical Steps and Intermediates

S.2.5 Process Validation and/or Evaluation

S.2.6 Manufacturing Process Development

NCE/Known chemical active substances

S.2.1 Manufacturer(s):

Name of manufacturer (& also plant if relevant) and country.

S.2.2 Description of manufacturing process and process controls:

Flow diagram (incorporate it if possible, rather than present in an Annex) with indication of the critical steps.

Indicate proposed commercial batch size and discuss batch size from batches provided, if necessary.

Alternate processes – if mentioned, include comment.

Reprocessing – if mentioned, include comment (e.g., when could this occur).

Catalysts and solvents - include comment if not in the main application (but in ASM Restricted part of an ASMF).

S.2.3 Control of materials:

State adequacy/extent of proposed specifications with particular mention of control of all impurities (including solvents), which might influence the quality of the active substance, especially if the impurities are not controlled in the ASS. Comment if of biological origin.

S.2.4 Controls of critical steps and intermediates.

Discuss the adequacy of the proposed process control.

S.2.5 Process validation

Brief summary of the extent of data and results.

S.2.6 Manufacturing process development -

Brief summary of the extent of data and results with reference to substance used preclinical/clinical studies if applicable.

Is a Design Space being proposed? Has the relationship between the process inputs (material attributes and process parameters) and the critical quality attributes of the active substance been established in a multivariate manner? The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. If a Design Space is proposed, please consult Annex III.

In general, critical statements are needed on the adequacy of the description of the synthesis, of the control of the materials and intermediates, reproducibility of the manufacturing process identifying those issues not adequately covered and which need to be addressed in the LoQ (with reference to number if wanted). Identify ‘Major’ issues.

Biotechnological medicinal products

S.2.1 Manufacturer(s)

• List of manufacturers. Identify manufacturers for which comparability issues or other quality issues have been raised. Highlight potential issues concerning compliance with the Rules on the Good Manufacturing Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission (e.g. transportation between sites...).

S.2.2 Description of Manufacturing Process and Process Controls

Provide summary of manufacturing process and in-process controls (specially those related to the safety of the product, e.g. tests for adventitious agents, RT activity); highlight any re-processing.

Provide summary for lifetime and sanitization procedures for chromatographic columns used during the purification process; assessment in relation to any impact on product safety.

Critical assessment of the adequacy of the development, consistency and control.

For a similar biological medicinal product, attention should be drawn to major differences with the process of the reference product, which could affect quality attributes, as appropriate.

S.2.3 Control of Materials

Information on the development genetics including origin of the gene, description of the gene construction, rationale behind the gene construct, genetic stability (specify state of the recombinant gene and copy number).

Description of the producer strain /cell line (type, origin), history of establishment and identification. Highlight any issues related to components used during development with potential impact on product safety (e.g. reagents of biological origin).

Cell banks: Establishment of the MCB/WCB, adequacy of tests performed, cell bank stability, phenotypic and genotypic characterization, protocol for the establishment of future WCB.

For of biological materials (e.g. monoclonal antibody purification columns, blood/plasma derivatives) used in the manufacture of the active substance, the assessment of the source, manufacture, characterization and control should be provided. For biological materials (e.g. blood/plasma derivatives such as human albumin) used in the manufacture of the active substance, the assessment of the source, manufacture, characterization and control should be provided. Plasma products such as human albumin that whenever it is used in the manufacture of medicinal products, it should comply with the Union guidance and should have the same documentation, including the origin of donations, the same quality and specifications as that of albumin for therapeutic use.

Make reference to A2 regarding adventitious agents/viral safety linked to source materials; highlight any issues related to TSE risk evaluation.

S.2.4 Controls of Critical Steps and Intermediates

End of production / cultivation criteria /definition of a batch.

Proposed intervals of set-point specifications and limits of IPC specifications in relation to the results of process validation.

Include description of storage conditions/shelf life of intermediates.

Highlight any specific step aimed/validated for virus removal/inactivation (e.g. low pH treatment).

S.2.5 Process Validation and/or Evaluation

Critical assessment of the adequacy of the validation of the manufacturing process; specify parameters tested and their relevance for the product concerned.

Re-processing should be specifically included or excluded.

Make reference to A2 regarding adventitious agents/viral safety linked to source materials.

Removal of impurities (process and product-related): assessment of the adequacy.

S.2.6 Manufacturing Process Development

• Assessment of history of development of manufacturing process and discuss impact on comparability (e.g. batches used for clinical trials vs commercial batches...) making reference to S.4.4.

Description of changes and reasons for changes (justification) with respect to the impact on quality.

Critical assessment of the significance of changes.

3.3. Characterization (CTD module 3.2.S.3)

Under this heading, the following CTD Headings would be discussed:

S.3.1 Elucidation of Structure and other Characteristics

S.3.2 Impurities

NCE/ Known chemical active substances

S.3.1. Elucidation of structure and other characteristics:

Summary of methods used to elucidate the structure and characterise properties of the active substance, e.g., chirality, polymorphism, etc.

In the case of radiopharmaceuticals, it should be made clear what the active substance is considered to be, i.e. unlabelled ligand, radiolabelled substance, or radiolabel for labelling of

another ‘carrier’ molecule. (In this latter case information is normally included in the ‘carrier’ dossier).

In general, critical statements are especially needed on the issue of whether or not methods used for elucidation of structure are adequate.

S.3.1. Impurities,

including process-related impurities & degradation products & solvents, reagents, etc – refer to text in QOS for this summary of data. Link to stability data & S.4.

For radiopharmaceuticals, mention also radiochemical purity and radionuclidic purity.

Differentiate, when possible, between process related impurities and impurities resulting from the degradation of the API.

Conclusion on the adequacy of the company’s approach to the control and qualification of impurities, with particular reference to non-clinical (toxicology) and clinical studies.

Biotechnological medicinal products

For a similar biological medicinal product, a fundamental part of the comparability exercise for quality will be the comparison of characterization data. This should consider structural identity and impurity profiles versus the reference product as appropriate.

Under S.3.1 include:

- Physicochemical properties.
- Determination of the composition, physical properties, and primary structure, information on higher-order structure.
- Pattern of heterogeneity (regarding product – related substances) and demonstration of its consistency biological activity.

Validity of the assay to measure the biological activity should be demonstrated.

Correlation between the biological assay and the clinical response should be established.

Potency (expressed in units). Results of biological assays should be expressed in units of activity calibrated against an international or national or in house reference material.

Where physicochemical tests alone are used to quantitate the biological activity (based on appropriate correlation), results should be expressed in mass immunochemical properties.

When the product itself is an antibody, its immunological properties should be fully characterized.

For proteins, immunocochemical properties may serve to establish its identity, homogeneity or purity or serve to quantify it.

Quantity. Quantity expressed in mass is a physicochemical measure of protein content.

Purity (including product-related substances). The active substance can include several molecular entities or variants which are considered product-related substances: individual and/or collective acceptance criteria for product-related substances should be set as appropriate.

Under S.3.2 (impurities) include the following:

Impurities should be characterized to the extent possible and, where possible, their biological activities should be evaluated.

Acceptance criteria for impurities (individual and/or collective) should be based on data obtained from lots used in preclinical and clinical studies and manufacturing consistency lots.

Process-related. Process-related impurities encompass those that are derived from the manufacturing process, i.e., cell substrates (e.g., host cell proteins, host cell DNA), cell culture (e.g. inducers, antibiotics, or media components), or downstream processing.

Product-related. Product-related impurities (e.g., precursors, certain degradation products) are molecular variants arising during manufacture and/or storage, which do not have properties comparable to those of the desired product with respect to activity, efficacy, and safety.

Note: Contaminants include all adventitiously introduced agents not intended to be part of the manufacturing process and as such should be discussed in Appendix A.2.

Comparability

3.4. Control of active substance (CTD module 3.2.S.4)

Under this heading, the following headings would be discussed:

S.4.1 Specification

S.4.2 Analytical Procedures

S.4.3 Validation of Analytical Procedures

S.4.4 Batch Analyses

S.4.5 Justification of Specification

NCE/Known chemical active substances

S.4.1. Specification:

Table of specification to be inserted. Provide a compiled specification when there are more than one sources of the active substance having different specifications.

S.4.2. Analytical procedures:

Combine in above table – just refer to method.

S.4.3. Validation of analytical procedures:

State if in accordance with Union guidelines or not, and mention any deviation.

Are the methods adequate to control the substance on a routine basis?

S.4.4. Batch analysis results (n=?);

do these confirm consistency & uniformity of the product? Do they indicate that the process is under control?

S.4.5 Justification of Specification

Is the applicant's proposed justification of the specification adequate or not, bearing in mind the intended use of the active substance in the product.

If real time release testing is proposed, has the applicant demonstrated enhanced product and process understanding? Has the applicant introduced appropriate controls of the critical process parameters and critical materials attributes that would justify real time release testing? When comparing batch results from end product testing and real time testing has the effect of environmental factors been considered? Is a scheme that foresees comparison of end product and real time release testing for a sufficient number of batches per year included? If multivariate models are used to predict the active substance quality attributes or for online process monitoring see Annex 3.

Biotechnological medicinal products

Under S.4.1 include:

Appearance and description. A qualitative statement describing the physical state (e.g., solid, liquid) and color of a active substance should be provided.

Identity. The identity test(s) should be highly specific for the active substance and should be based on unique aspects of its molecular structure and/or other specific properties. More than one test (physicochemical, biological and/or immunochemical) may be necessary to establish identity.

Purity and impurities. The absolute purity of biotechnological and biological products is difficult to determine and the results are method-dependent. Consequently, the purity of the active substance is usually estimated by a combination of methods. The choice and optimization of analytical procedures should focus on the separation of the desired product from product-related substances and from impurities. The impurities observed in these products are classified as process-related and product-related.

Potency. A relevant, validated potency assay should be part of the specifications for a biotechnological or biological active substance and/or finished product. When an appropriate potency assay is used for the finished product, an alternative method (physicochemical and/or biological) may suffice for quantitative assessment at the active substance stage. In some cases, the measurement of specific activity may provide additional useful information.

Quantity. The quantity of the active substance, usually based on protein content (mass), should be determined using an appropriate assay. The quantity determination may be independent of a reference standard or material.

In cases where product manufacture is based upon potency, there may be no need for an alternate determination of quantity.

The active substance specification should be included in or appended to the AR.

Under S4.3 include:

Adequacy of the validation of analytical methods.

Under S4.4 include:

Information on batch-to-batch consistency.

Consistency of the pattern of heterogeneity (e.g. glycoforms, isoforms) should be demonstrated.

Discussion of differences, if any, in impurity levels in pre-clinical, clinical and production batches.

Under S.4.5 include:

The rationale used to establish the acceptable range of acceptance criteria should be described, taking into account the overall manufacturing and purification process and the analytical procedures utilised. Acceptance criteria should be established and justified based on data obtained from lots used in preclinical and/or clinical studies, data from lots used for demonstration of manufacturing consistency, and data from stability studies, and relevant development data.

In some cases, testing at production stages rather than at the active substance or finished product stages may be appropriate and acceptable. In such circumstances, test results should be considered as in-process acceptance criteria and included in the specification of active substance or finished product in accordance with the requirements of the regional regulatory authorities.

The evaluator should assess whether the MAA has chosen the appropriate set of test methods to be routinely applied to active substance specifications out of the larger number of methods used during the development and characterization phases.

3.5. Reference standards of materials (CTD module 3.2.S.5)

NCE/Known chemical active substances

Are reference standard(s) available from main pharmacopoeias in accordance with the Eurasian Economic Union Member States Pharmacopeia Harmonization Conception?

Biotechnological medicinal products

For drug applications for new molecular entities, it is unlikely that an international or national standard will be available.

At the time of submission, the manufacturer should have established an appropriately characterized in-house primary reference material, prepared from lot(s) representative of production and clinical materials. In-house working reference material(s) used in the testing of production lots should be calibrated against this primary reference material.

Where an international or national standard is available and appropriate, reference materials should calibrate against it. While it is desirable to use the same reference material for both biological assays and physicochemical testing, in some cases, a separate reference material may be necessary.

Also, distinct reference materials for product-related substances, product-related impurities and process-related impurities, may need to be established.

When appropriate, a description of the manufacture and/or purification of reference materials should be included in the application. Documentation of the characterization, storage conditions and formulation supportive of reference material(s) stability should also be provided.

For a similar biological medicinal product comparison at the level of the active substance is required. Confirmation should be given that active substance from the reference products as stated in Section 3.2.P.6, was used as appropriate.

3.6. Container closure system (CTD module 3.2.S.6)

Is the choice of the container/closure justified, bearing in mind the physical/chemical properties of the active substance?

Does it provide adequate protection from microbial contamination, if this is considered to be necessary?

Confirm that the containers proposed for routine storage are those which have been used in the stability studies supporting the re-test period (ref. S.7).

3.7. Stability (CTD module 3.2.S.7)

Under this heading, the following CTD Headings would be discussed:

S.7.1 Stability Summary and Conclusions

S.7.2 Post-approval Stability Protocol and Stability Commitment

S.7.3 Stability Data

State if the studies are carried out in accordance with current ICH/Union guidelines. Are there deviations? Are the deviations justified in this case?

Stability summary and conclusions: Reference to any differences in manufacturing. Processes used, with comments on whether or not this has a significant effect on the stability profile.

Discuss the relevance of the protocol, particularly with regard to the parameters tested in the studies.

Confirm that the analytical methods are stability-indicating (ref. S.4). Stability indicating tests should be chosen, which are able to detect significant changes in the quality of the product.

Particularly for NCE's or known chemical active substances, confirm that the containers used in the stability studies are the same as those proposed for routine storage (ref. S.6).

Final conclusion on whether or not the proposed re-test period is justified.

4. Finished medicinal product (CTD module 3.2.P)

4.1. Description and composition of the finished product (CTD module 3.2.P.1)

All components of the presentation as intended for marketing, including reconstitution diluents, medical devices, etc. should be clearly stated.

In particular where the product presentation includes a medical device, it is important to cross-refer to the details of the device in 3.2.R, Regional Information. Check that any medical devices are authorized for marketing in the Union or have Union medical device authorization mark in accordance with the special mark authorizing marketing in the Union. Has this mark been attributed for the intended use?

Whilst the composition may be obvious, it may be necessary to pay particular attention to the details of the container/closure system, especially for labile or sterile products.

For a similar biological medicinal product, attention should be drawn to major differences in composition of the reference product as appropriate.

4.2. Pharmaceutical development (CTD module 3.2.P.2)

Under this heading, the following CTD Headings would be discussed:

P.2.1 Components of the finished product

P.2.1.1 Active Substance

P.2.1.2 Excipients

P.2.2 Finished Product

P.2.2.1 Formulation development

P.2.2.2 Overages

P.2.2.3 Physicochemical and biological Properties

P.2.3 Manufacturing Process Development

P.2.4 Container Closure System

P.2.5 Microbiological Attributes

P.2.6 Compatibility

Components of the Finished Product

Active Substance: Has the company identified those physicochemical properties of the active substance that are clinically relevant for the patient?

Have these properties been adequately specified and are they adequately controlled?

On what basis have the limits been justified?

The identification of the active substance attributes that may impact the finished product critical quality attributes may be performed on an empirical level or through systematic evaluation using risk assessment methodologies and statistically designed experimentation. In the latter case, please consult Annex 3.

Where potentially key parameters are not controlled, is the justification for their omission acceptable?

Use of materials of animal or human origin – have these been justified?

Excipients

Have important, novel or unusual excipients been identified regarding their impact on product performance?

The applicant's choice and function of key excipients should be mentioned, e.g. those modifying release or disposition of the active substance. In some cases (e.g. gas dispersions for diagnostic ultrasound investigations) the total formulation or system is responsible for the clinical efficacy of the product and these cases should be discussed in detail.

Is the quantity of the excipients used justified? (preservatives, buffers, etc)

The identification of the active substance attributes that may impact the finished product performance may be performed on an empirical level or through systematic evaluation using risk assessment methodologies and statistically designed experimentation. In the latter case, please consult Annex 3.

Assessors should also refer to section 4 of this report (CTD Appendix 3.2.A.3, Novel Excipients), where a more detailed evaluation of the excipient per se may be given. Note that 'new' excipients not present in products authorized in the Union or Member States may be regarded as new active substances and data requirements are 'full', i.e. manufacture and control, reference to toxicology studies, etc.

Finished Medicinal Product

Formulation Development: Has the applicant presented the Target Product Profile of the product, i.e. the quality characteristics that the product should have to ensure the desired quality taking into account safety and efficacy? Is the formulation development supported by clinical development? Discussion of bioequivalence between commercial formulation and clinical trial formulations, if different. Discuss if possible differences in finished product quality attributes (e.g. impurity and dissolution profile) in case of different strengths or a line extension. Discussion of the development of the dissolution test method, description of changes, demonstration of discriminatory properties. Results of studies to establish IVIVC, if relevant. Early development formulations for pre-clinical and clinical studies should be highlighted where relevant, and comments made relating to the findings of these studies. Additional details should be given if the development encompasses a paediatric formulation including information for which age group this is intended, if appropriate.

Overages. On which basis are overages justified?

Physicochemical and Biological properties. • Are key parameters identified and adequately controlled?

The Module 3 gives an adequate list of parameters that need to be discussed with regard to their impact on the performance of the product, where relevant, e.g. for tablets – the particle size and polymorphism of an active substance with low aqueous solubility may need to be discussed with reference to their effects on dissolution and bioavailability. In this example the pH-

solubility profile would also be relevant basic information having an impact on the choice of dissolution test methodology.

Manufacturing Process Development:

If the manufacturing process of the product influences the physicochemical properties of the active substance (e.g. polymorphic form), check that the studies carried out on the active substance remain valid.

Has the choice of process been justified, where necessary? Are critical process parameters, relevant for subsequent process validation, identified? Are differences in the manufacturing processes of the commercial product and clinical trial material adequately explained and discussed? Does the process compensate for the variability in the material attributes?

The identification of the critical process parameters may be performed on an empirical basis or through systematic evaluation using risk assessment methodologies and statistically designed experimentation. In the latter case, please consult appropriate guidance.

Container Closure System:

Is the choice of materials for the container and closure adequate to support the stability and use of the product with its targeted patient group (e.g. elderly, child resistant)?

Technical properties of the container closure system with respect to patient use should be considered, e.g. nasal sprays, inhalers, prefilled syringes.

Microbiological Attributes: Is the use of additives, e.g. preservatives and antioxidants justified regarding their concentration and nature?

Compatibility:

Do the compatibility studies support the instructions for use and handling in the SPC?

4.3. Manufacture of the finished medicinal product (CTD module 3.2.P.3)

Under this heading, the following CTD Headings would be discussed:

P.3.1 Manufacturer(s)

P.3.2 Batch Formula

P.3.3 Description of Manufacturing Process and Process Controls

P.3.4 Controls of Critical Steps and Intermediates

P.3.5 Process Validation and/or Evaluation

The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in the manufacturing and testing should be provided.

Description of manufacturing process and process controls: Flow diagram (incorporate it if possible, rather than present in an Annex) with indication of the critical steps.

Has the applicant introduced controls to monitor real time the critical material attributes and critical process parameters? Do the controls reduce the risks identified during formulation and process development? Are there feedback loops in place that allow adjustment of the process to compensate for the variability observed?

Is a Design Space being proposed? Has the relationship between the process inputs (material attributes and process parameters) and the critical quality attributes been established in a multivariate manner? If a Design Space is proposed please consult Annex III.

Where the product consists of the active substance without excipients details of the manufacturers should also be referred to here and should be accordingly licensed.

Where ranges of batch size are proposed for production, blending of batches or the use of sub batches, the acceptability should be addressed. Discuss the bath size(s) of the data provided.

The assessor should discuss any specialized processes that may need to be inspected (see preamble to this report).

Confirm that process holding times and transport arrangements are relevant and have been justified / validated.

The assessor should comment here on whether process validation data are needed in the dossier (i.e. whether it is needed prior to authorization). Where non-standard methods are used

these validation data would normally be expected. For standard processes the process validation scheme referred to in 3.2.R Regional Information should be evaluated.

Any proposals for continuous process verification should be supported by adequate development data and an appropriate control strategy that allows real time monitoring of the critical process parameters and material critical quality attributes.

Any requests for 'parametric release' need to be fully evaluated and commented on here, with a comment from the GMP Inspectors, where necessary, in accordance with the Union guidance.

Where relevant, the safety of the product in respect of transmission of 'adventitious agents' should be considered under Appendix A.2 Note: This is perhaps more relevant for biotech/biological products.

4.4. Control of excipients (CTD module 3.2.P.4)

Under this heading, the following CTD Headings would be discussed:

P.4.1 Specifications

P.4.2 Analytical Procedures

P.4.3 Validation of Analytical Procedures

P.4.4 Justification of Specifications

P.4.5 Excipients of Human or Animal Origin

P.4.6 Novel Excipients

If monograph of the Pharmacopoeia of the Union exists, mention may be brief and should be enough in most cases.

If non-Union Pharmacopoeia, is the specification adequate?

Do the specifications and tests reflect the functionality in a relevant way? Especially in novel delivery systems, some ingredients may have a special function, and should be described and controlled in more detail, especially with regard to functionality testing.

For biological materials (e.g. blood/plasma derivatives such as human albumin) used in the manufacture of the finished product, the assessment of the source, manufacture, characterisation and control should be provided. The note for Union guidance on Plasma-Derived Medicinal Products indicates that for plasma products such as human albumin that whenever it is used in the manufacture of medicinal products, it should comply with the guidance and should have the same documentation, including the origin of donations, the same quality and specifications as that of albumin for therapeutic use.

Make reference to A2 regarding adventitious agents/viral safety linked to excipients; highlight any issues related to TSE risk evaluation.

Note that 'new' excipients not present in products may be regarded as new active substances and data requirements are 'full', i.e. manufacture and control, reference to toxicology studies, etc.

4.5. Control of finished medicinal product (CTD module 3.2.P.5)

Under this heading, the following headings would be discussed:

P.5.1 Specification(s)

P.5.2 Analytical Procedures

P.5.3 Validation of Analytical Procedures

P.5.4 Batch Analyses

P.5.5 Characterization of Impurities

P.5.6 Justification of Specification(s)

Specification: Release and shelf life specifications should be presented side by side in tabular form, with brief reference to the method used.

If real time release testing is proposed, has the applicant demonstrated enhanced product and process understanding? Has the applicant introduced appropriate controls of the critical process parameters and critical materials attributes that would justify real time release testing? When comparing batch results from end product testing and real time testing has the effect of environmental factors been considered? Is a scheme that foresees comparison of end product and real time release testing for a sufficient number of batches per year included? If multivariate

models are used to predict finished product quality attributes or for online process monitoring see Annex 3.

Specification summary, important tests, particularly relating to bioavailability/efficacy (e.g. dissolution, particle size, polymorphism if relevant.) and safety (impurities or sterility, pyrogens etc. for sterile products). The general relevance of the release specification should be discussed considering the method of manufacture and clinical use, route of administration etc.

Validation of analytical procedures: State if in accordance with ICH or not, and mention any deviations. (All control methods, regardless of whether they are applicable to control at release or to the shelf life should be discussed here, under P.5).

Note that the tests for impurities in the product specification should focus on degradation products arising from the manufacturing process and those expected during storage, rather than manufacturing process-related impurities carried over in the active substance if these are controlled in the active substance and do not change in the product during storage.

Batch analysis results (n=?); do these confirm consistency & uniformity of the product? Do they indicate that the process is under control?

For radiopharmaceuticals, a discussion of radiochemical purity of reconstituted 'cold' kits should be discussed, where relevant.

For biotechnological products, the important key elements described for specification of active substance are also in many cases applicable for the finished product.

4.6. Reference standards or materials (CTD module 3.2.P.6)

(See S5 where relevant)

NCE/Known chemical active substances

Are reference standard(s) available from main pharmacopoeias in accordance with the Eurasian Economic Union Member States Pharmacopeia Harmonization Conception?

For a similar biological medicinal product, the following information regarding the reference product should be provided in a table: Name, strength, pharmaceutical form, MAH, batch number and country of origin of the batches used in the comparability exercise (the reference product must be from a rigorously regulated pharmaceutical market).

4.7. Container closure system (CTD module 3.2.P.7)

Is the choice of the container/closure justified, bearing in mind the physical/chemical properties of the product?

Does it provide adequate protection from microbial contamination, if this is considered to be necessary?

Confirm that the containers proposed for routine storage are those which have been used in the stability studies supporting the shelf life. (ref. CTD.3.2.P.8).

4.8. Stability (CTD module 3.2.P.8)

Under this heading, the following headings would be discussed:

P.8.1 Stability Summary and Conclusion

P.8.2 Post-approval Stability Protocol and Stability Commitment

P.8.3 Stability Data

State if the studies are carried out in accordance with current Union guidelines. Are there deviations? Are the deviations justified in this case?

Discuss the relevance of the protocol, particularly with regard to the parameters tested in the studies. Bracketing & Matrixing designs – acceptable?

Are the methods used the same as or different to those described in P.5? Are they well validated and shown to be stability indicating?

Confirm that the containers used in the stability studies are the same as those proposed for routine storage.

Note that the qualification of impurities carried out on the active substance may not necessarily address degradants induced by the product matrix or product manufacturing process.

In addition, other product characteristics may change on storage and these need to be justified with reference to the preclinical and clinical results.

Confirm if the proposed shelf life and storage conditions are adequate.

In–Use stability:

Comment also on stability after opening and during use, e.g. for infusions to be diluted, stability after dilution and during administration, compatibility with commercially available administration equipment, etc. Are an in-use shelf life and storage conditions necessary? Are the applicant's proposals in line with the current guidelines? If not, are they still justified?

For radiopharmaceuticals, a discussion of user-reconstitution methods for 'cold' kits may be discussed here, together with a discussion of post-reconstitution stability.

General:

Are all of the above considerations correctly reflected in the SPC/package leaflet? Conclusions on whether or not all shelf lives and storage conditions defined in the SPC are justified.

5. Appendices (CTD module 3.2.A)

A.1. Facilities and equipment

A.2. Adventitious agents safety evaluation

A.2.1. Non-viral adventitious agents

A.2.1.1. Control of mycoplasma, bacteria and fungi

A.2.1.2. Risk of contamination with animal TSE

1.1 Control of mycoplasma, bacteria and fungi:

Cross-references to other parts of the assessment report (manufacturing process etc.) should be provided.

If non-pharmacopoeial methods are used for bacterial, mycoplasmal and fungal testing, these methods should be assessed.

If, for specific reagents or substances problems with respect to sterility have been identified, a detailed assessment should be conducted.

1.2. Risk of contamination with animal TSE:

Materials which fall within the scope of the TSE Note for Guidance, should be identified (reference to Table A) and TSE compliance should be demonstrated by the applicant, by TSE certification and/or via scientific documentation. (It may be useful to present a summary of the most important information in a table).

Assessment of documentation for compliance with the Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products, if necessary.

Conclusion.

A.2.2. Adventitious viruses

2.1 Identification of materials of biological origin

The assessment report should include a short description or listing of materials of biological origin which are introduced, or come into contact with, the product during production, summarising the characteristics of the materials with regard to the possibilities for virus contamination. Cell substrates, reagents used or introduced directly or indirectly (e.g. affinity chromatography materials), as well as excipients should be considered. (Some of the required information may be found in the dossier under 3.2.S.2.3. Control of Materials, and under 3.2.P.4.5. Excipients of Human or Animal Origin)

2.2 Testing of the source materials

Cell line characterisation. The tests conducted should be tabulated. Tables should indicate which tests have been performed on which cells (MCB, WCB, EOP). Cell lines used for in-vitro testing on adventitious viruses should be identified, MAP/HAP tests need not to be described in detail, but in-vivo testing should indicate the animals used and, if relevant, the route of administration. Were three batches of unprocessed bulk tested for the presence of adventitious viruses?

Reference to Plasma Master File or assessment of the plasma master file data, if necessary. (Plasma derivatives)

The assessment report should address controls on donors, donated tissues, and cell banks. (Products derived from human cell tissue).

Are all relevant Pharmacopoeia of the Union and WHO tests and controls intended to exclude contamination with specific and non-specific extraneous agents applied? (Virus vaccines)

In the light of the information provided in point 2.1, has the applicant done an appropriate investigation of viral contamination?

2.3 Routine testing on unprocessed bulk (if applicable)

Is a routine testing of unprocessed bulk required? Is the testing regime appropriate and adequate? (Cell derived products).

In the light of the information provided in point 2.2, has the applicant developed an appropriate strategy for routine testing?

2.4. Testing of purified bulk (if applicable)

Has the applicant provided an acceptably justified regime for routine/not-routine testing the purified bulk?

2.5 Viral clearance studies

General remarks to the design of the study

Are virus clearance steps required for the product?

Is the choice of process steps for virus clearance appropriate and sufficient?

Is the choice of viruses acceptable?

In principle, are the studies performed according to the recommendations of the guidelines?

2.5.1 Assessment of the validation studies according to the different stages of manufacture which have been studied:

1) Is the manufacturing process adequately represented in the laboratory-scale experiments?

Are the important process parameters compared and convincingly reproduced in the down scale process?

Is appropriate down scaling confirmed by the analytical data of the intermediate products/fractions used?

In the case of chromatographic steps, are the parameters (bed height, loading, flow rates (cm/min) for all steps during the process, loading, elution profiles) comparable?

Is the post-elution fraction (wash) as well as the high salt fraction, if appropriate, tested for virus content? Are the parameters reported for each run?

If columns are proposed for re-use, are the conditions of sanitization and re-use of column reported and validated?

In the case of filtration steps, are the parameters (volume/filter area, flow rates or pressure and/or transmembrane pressure) identical to the manufacturing process? Do the clearance studies adequately reflect the different stages of the filtration process during manufacture (filtration/ultra filtration or washing out of the product) and are these stages appropriately investigated?

Deficiencies should be identified.

2) Are the virus clearance experiments convincing?

Are the possibilities for material cytotoxicity, and interference with the virus assays, tested?

If filtration processes are evaluated, are virus aggregates tested for, and excluded by appropriate procedures?

Are raw data provided and taken into account in the calculation of the reduction factors?

Any deficiencies should be identified.

3) Assessment of claimed virus reduction factors (Rf)

Are claimed Rf values convincing and adequately supported by the data?

A table summarizing the reduction factors should be included (amended values, if necessary).

Is the robustness (influence of important procedural parameters) of the manufacturing step investigated?

Has it been demonstrated that the validated virus clearance steps are able to eliminate substantially more virus than is potentially present in a single-dose equivalent of unpurified bulk.

Summary of A.2.2.5

A table of the reduction factors for the whole process should be provided (amended values, if necessary).

The assessment should be summarized.

A.2.3. Conclusion of 5.2

Overall summary and conclusion should be provided on:

Sterility (bacterial, fungal, mycoplasmal)

TSE safety

Viral safety

A.3. Novel excipients

Note that 'new' excipients not present in products authorized in the Union may be regarded as new active substances and data requirements are 'full', i.e. manufacture and control, reference to toxicology studies, etc. (Detailed assessment of these special new excipients should be discussed here).

6. Regional information

Process validation scheme for the finished product

Medical device issues

Where the presentation of the medicinal product includes elements which are classified as medical devices (e.g. needles, catheters, etc.), these must be medical device-marked prior to submission of the dossier and a statement on compliance with the relevant medical devices legislation is required. Otherwise, to complete the evaluation of the product as a whole, the medicines competent authority has to consult with a medical devices competent authority in order to verify the acceptability of the device element with regard to Union requirements. In addition, for those cases where the device may not be so simple, but may in fact be a complex delivery system (e.g. transdermal iontophoretic delivery system included in the total presentation) an evaluation report on the device aspects in relation to the clinical performance of the product as a whole would also be necessary.

TSE issues

7. Assessor's comments on the SmPC, labels and package leaflet

8. Assessor's overall conclusions on quality

The content of this paragraph could be carried forward to the overview assessment report on safety, quality, and efficacy of the assessment.

A self-standing and focused elaboration might therefore be necessary to allow the reader comprehensive access to the relevant findings thus enabling adequate benefit risk assessment.

In relation to the Quality aspects impacting the Benefit-Risk balance, indicate if there is any quality aspect either in the active substance or in the finished product which could lead to impact on the Benefit-Risk Balance.

Indicate if a paediatric formulation has been developed or is to be developed. Indicate in which paediatric age groups the formulation would be used.

As an alternative this section could simply state the main conclusions, in which case the text in the overview assessment report on safety, quality, and efficacy has to be elaborated on separately.

Highlight any areas of agreement/disagreement with the “quality overall summary” in the submitted dossier. With respect to a paediatric formulation, indicate if there is a need to request an Opinion from the assessors of national competent authorities.

9. List of questions as proposed by the assessor

Definitions of questions:

“Major objections”, preclude a recommendation for marketing authorization. In principle, one major objection may entail more than one question and the use of bullet points or subheadings is encouraged. It is vital that the structure and content of a major objection are clear and understandable to the reader. Detailed comments may be necessary along with a reference to Union guidance documents.

Ideally, the objection should include a clarification as to what kind of response/action from the applicant.

“Other concerns”, may affect the proposed conditions for marketing authorization and product information. Other concerns should be resolved before approval. Failure to resolve other concerns may render the application un-approvable.

In general, subheadings should be used where necessary throughout the list, to collect objections and concerns in relevant groups.

This list should be carried forward to the overview assessment report on safety, quality, and efficacy.

Quality aspects

Major objections

Active substance [related to additional data provided by applicant only]

Active substance [applicant’s part as provided by ASMF holder]

Note:

1. In case the ASMF procedure is used the following should be stated in case potential serious risks to public health are being raised on the restricted part of the ASMF: “For potential serious risks to public health on the restricted part of the ASMF see separate AR on the ASMF”.

In addition, mention if there are additional major objections on the active substance concerning the confidential / closed part of an ASMF. These will be detailed in an annex to the main Quality Report (see Appendix 8 to the Rules of authorization and assessment of medicinal products for human use subject to approval by the Eurasian Economic Commission).

Finished product

Other concerns

Active substance [related to additional data provided by applicant only]

In addition, mention if there are additional concerns on the active substance concerning the confidential / closed part of an ASMF. These will be detailed in an annex to the main Quality Report.

Note: When applicable: “For other concerns on the restricted part of the ASMF see separate AR on the ASMF”

Finished product

Recommendations

This section shall contain assessor’s comments/conditions which do not preclude granting a marketing authorization and which might be resolved having the marketing authorization been granted using variation to a MAA procedure

10. Annex 1 (as appropriate)

Active Substance Master File (ASMF)

Assessment Report(s) – in separate document(s).

11. Annex 2: Design Space and Post-approval change management protocol

The purpose of this Annex is to highlight issues that should be reflected in the assessment report concerning the evaluation of risk assessment methodologies and statistical tools that are used in the context of appropriate Union guidelines. Assessors are encouraged to read this annex in conjunction with any related Union guidelines.

1. Risk assessment methodologies

Risk assessment tools can be used in many situations. For instance it may be used to rank and select material quality attributes and /or process parameters that should be within appropriate ranges to ensure the desired product quality. Such tools could also be used to select process parameters that may potentially impact product quality based on prior knowledge and experimental data. Issues that need to be taken into account in the evaluation include:

Has a summary of all material quality attributes and process parameters that based on previous knowledge and/or experimental data may have an impact on product quality been presented?

For FMEA analyses:

Have all the relevant known risk factors been included? e.g. known risk factors of the finished product (e.g. degradation, solubility etc)

Has the effect of unit operations and material properties been included?

Has the applicant explained how the risk ranking and scoring has been performed?

Has the applicant justified how the threshold has been set in order to select, which parameters will be further studied?

Do you agree with the proposed risk ranking?

Is the result of the FMEA in accordance with existing scientific knowledge? If not has it been justified?

Are the identified risks managed by the Design Space or the proposed control strategy?

2. Design of Experiments

Design of Experiments (DoEs) is a strategy for experimentation, whereby all factors under study are varied at the same time in accordance to rigorously formulated mathematical protocols. The goal is to generate representative and informative experiments that maximise the information provided with the minimum number of experiments. The factors to be studied in a DoE should come out of the risk assessment exercise. A full statistical evaluation of DoEs performed at early development stages (e.g. for screening) is not necessary. A narrative description of the factors and levels studied and the conclusions reached is adequate.

However for DoEs used for the establishment of CQAs, CPPs and / or a Design Space: The following data should be considered:

Type of experimental design used and justification of its appropriateness (e.g. some screening designs are not appropriate since they cannot identify interactions). The power of the design should be stated. (Experimental error compared to the differences in the responses that have to be shown)

Factors under study and their ranges (in a tabular format if possible)

The list of design runs clearly stating the batch or study number and the scale of the batch involved in each run. The number of replicated runs should be mentioned.

Reference to the analytical methods used for the evaluation of the data and demonstration of their suitability for their intended use.

Statistical results (e.g. Pareto diagrams or a simple list of the sizes of effects and interactions) showing the relative significance of the factors under study as well as of the interactions between them (where applicable) should be provided

Ensure that the predictions made from a DoE study are appropriate for the ranges studied and scale/equipment differences.

3. Multivariate Data Analysis (MVDA) for Multivariate Statistical Process Control (MSPC)

Multivariate data analysis (MVDA) including Principal Components Analysis (PCA) and Partial Least Squares (PLS) can be used to model pharmaceutical processes. PCA is often used for data overview e.g. for detecting groups and trends among observations, for evaluating relationships between variables and between observations and variables. While PLS is used for linking input and response variables together with the aim of predicting one or more components. Issues that need to be taken into account, when MVDA models are used for MSPC include:

Are the spectral sample preparation and the reference analytical method used to analyse the sample fit for purpose? For online or in-line control where there is no sampling: what is the repeatability and the reproducibility of the sampling in combination with the analytical method?

Are the validation (training) and calibration (test) datasets representative of the expected process variability? Has the applicability of the model been demonstrated across all the variation allowed by the Design Space? In the cases that this is difficult to show, the results of the risk assessment could be used. The influence of all important risk factors should be checked and included in the calibration, validation and test set.

Does the variability of the calibration (test) set adequately represent most of the variability of the validation (training) set?

Have outliers been identified in the original dataset and if yes, is the justification for (non)-omission of data valid? Please note that if the dataset used to develop the model is generated from a DoE, the omission of data may have a greater impact on the predictive power of the model compared to historical datasets.

Is the information concerning the pre-treatment of data (if any) adequately described and consistently applied for all datasets used for creation, optimization and validation of the model?

Are the MVDA modelling techniques adequately described including a brief justification for the selection of the selected algorithm?

Do you agree with the selection of the variables that have been included in the model? Compare with the results of the risk assessment. Are there any relevant sources of variation not included in the model and if yes, is this justified?

For PLS models, is the model fit for purpose? Is the complexity of the model optimal? Note: the PLS model complexity usually corresponds to the number of PLS (latent) factors resulting in the lowest RMSECV. The model complexity (number of PLS factors used to build the model) should be presented in a graph showing the regression coefficients for each variable

Can the weightings (high/ low) of the variables in the model be explained with the existing scientific knowledge or rational concerning that variable and/or manufacturing process?

Is the MVDA model statistically evaluated for fitting and predictive ability? The standard error for prediction should be discussed against the precision of the reference analytical method precision.

Has a model verification scheme been proposed for the product lifecycle? Has it been defined which criteria would trigger an update of the model and are they adequate?

4. Design Space (DS)

Aspects that may be considered when a DS has been proposed include:

Has the applicant provided adequate data to support the DS applied for? (Risk assessment, experimental data, models that have been statistically evaluated and verified at full scale)

In case that the Design Space has been developed at lab or pilot scale, has the applicant demonstrated its validity at production scale through the use of scaling factors or independent experiments, or otherwise has it been demonstrated that the parameters are scale independent? Scaling factors might be supported by literature or prior knowledge. Has the applicant discussed the potential risks in the scale-up operation and is there an appropriate control strategy in place to manage these risks?

Has the applicant considered all CQAs, when developing a DS? (See risk assessment and DoE results)

Does the control strategy support the DS?

Are all critical parameters identified in the unit operation part of the Design Space? If not, is there an appropriate justification?

12. Annex 3. Design space and change management protocols (if applicable)

This Annex is an extract of the main body of the AR and its purpose is to summarize all aspects agreed upon in the dossier that result to post approval regulatory flexibility. This annex may be used by Inspectors and could be a basis for the evaluation of post-approval variation applications.

1. Active substance

1.1. Design space for the active substance

(Presentation of the Design Space (attributes and their ranges) in a tabular format

1.2. Change management protocols for the active substance

(Description of the changes included in the agreed protocol as well as the agreed variation category for reporting the implementation of the change)

2. Finished product

2.1. Design space for the finished product

(Presentation of the Design Space (attributes and their ranges) in a tabular format

2.2 Change management protocols for the finished product

(Description of the changes included in the agreed protocol as well as the agreed variation category for reporting the implementation of the change)

APPENDIX 15
to the Rules of authorization
and assessment of medicinal products
for human use

GUIDANCE DOCUMENT
on the content of the critical assessment report on clinical aspects

I. GENERAL GUIDANCE

In general, the following aspects should be considered when drawing an critical assessment report on clinical aspects (hereinafter referred to as the report):

The report should be sufficiently detailed to allow for secondary assessment by other assessors of the competent authorities or organizations of the Member States of the Eurasian Economic Union (hereinafter referred to as Member States and Union, respectively).

The use of tables/graphs/figures is encouraged; examples are given in the template as laid down in Appendix 7 to the Rules of authorization and assessment of medicinal products for human use (hereinafter referred to as the Authorization rules) and are to be used as appropriate. Tables taken from the dossier may also be included into the assessment. Put appropriate footnotes.

Cross-references should be used to clearly indicate the origin of any information used in the report, such as the specific parts of the dossier (e.g. overview, summary, study reports), references to the literature or other sources.

Reference to information which is confidential and should not be seen by the applicant (e.g. reference to the assessment of another medicinal product) should be clearly marked as "Confidential" and highlighted using a yellow background. These sections will be removed before the assessment is sent to the applicant.

Separate pages have been added in the template for the inclusion of a list of abbreviations and a list of references, to be completed when necessary.

It is recommended that the font used in the main text be Times New Roman, size 11.

When drawing up the report other relevant documents for efficacy and safety evaluation shall be taken into account.

II. CLINICAL CRITICAL ASSESSMENT

For each main section of the assessment report for modules 4 and 5, the report should describe the data submitted.

Each basic section of the report shall contain data in accordance with Appendix 1 to the Rules. Types of studies in each section shall contain paragraph numbers (sections and subsections) in accordance with Appendix 1 to the Rules. For each type of study, after distinguishing between main and supportive data, it should be assessed whether the main data consist of all the particulars and documents of clinical study reports ("original data"), bibliographical references, a combination of the two, or if data are absent.

If data from publications is used by the applicant or in the context of the assessment, a clear referencing should be included allowing for clear identification of the publications. Consider generation of a reference list if a substantial number of publications is used. If

appropriate ensure clear expression of the view on the content of a publication (e.g. if used not only as data reference but in the context of a discussion).

Where the data submitted deviate from the requirements, the acceptability of any justifications should be assessed. In particular, absence of any data for non-clinical/clinical test or trials, or use of bibliographic references substituting in part or completely original data for main studies must be justified. See further guidance provided in the Overview template guidance document.

1. Introduction

1.1. Type of application and aspects on development

1.1.1. Type of Application:

Indicate type of marketing authorization application (reference to the legal basis of the application; complete/abridged. (For further guidance see overview template/guidance document), Indicate if acceptable justifications exist for waiving certain studies or replacing original studies by literature data. If certain studies are only available as publications it is important to clarify whether or not such studies are/are not of sufficient quality to allow an in depth assessment of crucial data.

Indicate if the applicant has requested a conditional marketing authorization or an approval under exceptional circumstances (or if this is proposed by the assessor). The assessment of the fulfilment of relevant criteria is an integrated part of this report.

For Conditional approval, the assessor shall assess the validity of the reason(s) put forward by the applicant according to the guideline for conditional Marketing Authorization pursuant to the Rules. Address the following: serious/life threatening disease; emergency threat; orphan product - positive R/B; medical need; does immediate availability outweighs the risks? For conditional approval the positive B/R is made pending results of further studies. Discuss those studies in terms of feasibility once the product is on the market.

For exceptional circumstances, the assessor shall assess the validity of the reason(s) provided by the applicant. For an approval under exceptional circumstances it is in principle not foreseen that the applicant can provide comprehensive data on efficacy and safety. Address particularly the relevant indent (rarity, ethics or stage of scientific knowledge) and the type of specific obligations/procedures that may be necessary.

1.1.2. Biosimilars

In the particular case of a “bio-comparability exercise”, the development strategy chosen by the company should be described, justified and assessed in view of the Rules of studying biological medicinal products in the Eurasian Economic Union subject to approval by the Eurasian Economic Commission.

For similar biological medicinal products, Appendix 1 of the Rules and the Rules of studying biological medicinal products in the Eurasian Economic Union subject to approval by the Eurasian Economic Commission have to be taken into consideration.

Finished product and active substance quality issues (Module 3) have to be taken into consideration An extensive comparability exercise will be required to demonstrate that the similar biological and reference products already authorized in the community have similar profiles in terms of quality, safety and efficacy.

Detailed information of the reference product (name) strength, pharmaceutical form, MAH, date of authorization in the Union and the detailed information (such as batch number and country of origin) of the batches used in the comparability exercise (quality, non-clinical and clinical): need to be provided in tabular format in the quality part of this report.

1.1.3. Aspects of development:

Comment on the clinical development program in view of the proposed indication and posologies. State whether the extent of studies conducted is in line with recommendations of the Union or Member State legislation.

Indicate whether a Paediatric Investigation Plan (with or without deferral) or a product-specific waiver has been agreed with the national competent authorities and assessment organizations, or whether a class waiver applies. Briefly summarize the conditions and principal requirements of the paediatric investigation plan with regard to clinical aspects, if applicable, and state the relevant key information about the current status of the clinical studies (i.e. completed, studies ongoing, etc.).

Indicate availability of development in other special populations such as in elderly, in males/females and in ethnic minorities. State the number and characteristics of healthy volunteers/patients/males/females included in the studies, as appropriate, (see further section III.1 for the inclusion of a more elaborate table which should be in accordance with CTD table 2.7.3.1 as appropriate).

State if, and when Scientific Advice / Protocol Assistance has been given, describe the issues and indicate whether the advice was followed by the applicant.

Indicate if, and when the product received Orphan Drug Designation related to the applied indication. If necessary, report on such a decision on products having similar mechanisms of action.

Drug development may have been performed considering the criteria for a conditional approval/exceptional circumstances and the assessment of the fulfilment of relevant criteria is an integrated part of this report (see above).

1.2. Compliance with the Rules of the Good Clinical Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission

Compliance with the Rules of the Good Clinical Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission should be addressed here and in section 3.1 and also in the overview assessment report on safety, quality, and efficacy.

In this section specifically address:

Any concerns raised during the assessment about compliance with the Rules of the Good Clinical Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission or related regulatory and ethical requirements (data accuracy or protocol compliance and compliance with ethical aspects).

Statement on application of ethical standards in clinical trials foreseen by the Rules of the Good Clinical Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission.

Discuss the need for an inspection for compliance with the Rules of the Good Clinical Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission.

Decision on inspection shall be maid based on several critical factors as laid down in the Rules taking into account the application as a whole. The list of critical factors is non-exhaustive; significance of each factor for making a decision on unscheduled inspection for compliance with the Rules of the Good Clinical Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission may largely depend on various parameters.

To trigger an inspection for compliance with the Rules of the Good Clinical Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission, you need to:

Contact your national pharmaceutical inspectorate.

Determine with them the clinical trial(s), sites and special concerns or issues to be addressed/the trigger or random factor related to the inspection.

Formulate the formal inspection request for review by the inspectors and agreement by the competent assessment organizations of the Member States for adoption by the competent authorities of the Member States and inclusion in the inspection plan (day 90 or 120 of the granting a marketing authorization).

For detailed information on inspection triggers, see the Rules and Rules of carrying out of pharmaceutical inspections of the Eurasian Economic Union.

1.3. Orphan medicinal products

Indicate if, and when the product received Orphan Drug Designation related to the applied indication. State the orphan indication and the prevalence of the condition (according to the Member States official statistics or official lists of orphan diseases subject to approval by Member States).

Introduce the following statement as appropriate: <According to <state the source> the prevalence of the “condition” <state the condition> is <state prevalence> per 10 000 individuals in <Member State.>

Special consideration may have to be given to orphan designated products with regard to the scope of the orphan condition in relation to the therapeutic indication claimed by the applicant.

2. Clinical pharmacology

2.1. Pharmacokinetics

2.1.1. Introduction

A short background information on study design (e.g. crossover/population pharmacokinetics), number and characteristics of patients/healthy volunteers included in the different studies and brief description of used validated assays should be given. PK data is usually obtained from healthy volunteers, as well as patients.

Comment on what is required for this specific product (e.g. NCE: full PK documentation), and on quality of clinical overview (expert report on Module 2) and compliance of PK studies with the Rules of the Good Clinical Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission.

Specifically address if pharmacokinetic data in the paediatric population is available (c.f. special populations).

Each section or subsection of the assessment report should contain 2 paragraphs:

a) The factual study results [Data from CTD modules 5.3.1, 5.3.2, 5.3.3 and PK/PD from 5.3.4 under relevant sub-headings], preferably in tables [with a reference to the clinical summary (module 2.7), individual reports or assessor’s table].

b) Include assessor’s comments where necessary.

The different studied pharmacokinetic parameters could be inserted into a single general summary table(s), in the introduction. When commenting on the different pharmacokinetic parameters, cross-reference may be made to this table(s).

Depending on the type of application, subheadings under ‘Pharmacokinetics’ may be deleted or changed, as appropriate.

For similar biological medicinal products the relevant Appendix 1 to the Rules and Rules of studying biological medicinal products subject to approval by the Eurasian Economic Commission have to been taken into consideration.

The clinical comparability exercise is a stepwise procedure that should begin with pharmacokinetic (PK) and pharmacodynamic (PD) comparative studies followed by comparative clinical efficacy trial(s) versus the chosen reference medicinal product authorized in the Union.

In certain cases, pharmacokinetic/pharmacodynamic (PK / PD) studies for demonstrating therapeutic equivalence is sufficient.

2.1.2. Methods

2.1.2.1. Analytical methods

Brief description of analytical methods used, with emphasis on the performance characteristics of assay validation and quality control.

2.1.2.2. Pharmacokinetic data analysis

Brief description of pharmacokinetic methods.

2.1.2.3. Statistical analysis

Brief description of statistical methodology.

2.1.3. Absorption

Data from CTD module 5.3.1 to 5.3.3 - if appropriate, studies are inserted here and tabulated whenever possible (e.g. rate and extent of absorption, involvement of active transport proteins in absorption).

2.1.3.1. Bioavailability

Data from CTD module 5.3.1.1 - reports on Biopharmaceutical studies are inserted here. Absolute and relative bioavailability.

Assessor’s comment

2.1.3.2. Bioequivalence

Data from bioequivalence studies between formulations used in clinical studies and final formulation to be marketed.

Reference should be made to bioequivalence studies carried out to address equivalence for manufacturing changes during the development and to justify changes between clinical trials formulation and finished product intended for marketing.

For biological or biotechnology products this part should be expanded to cross-refer also to pre-clinical and functional assays.

Comparative PK studies designed to demonstrate equivalence between the similar biological medicinal product and the reference product with regard to key PK parameters are an essential part of the comparability exercise.

The reference product (used in clinical trials) should be indicated and it should be clear if the reference product is authorized in the Union.

2.1.4. Distribution

Volume of distribution, protein binding in-vitro and ex-vivo, distribution to tissues and red blood cells.

2.1.5. Elimination

Elimination route (metabolism, excretion unchanged renally and biliary), clearance, half-life.

2.1.5.1. Excretion

Routes of excretion of the product. Fraction of the amount of product that is excreted unchanged. Involvement of active transport proteins for products that are renally secreted.

2.1.5.2. Metabolism

Identification of metabolites, extent of metabolism, metabolic routes, enzymes involved in metabolism. Contribution of metabolites to effect. Data from in-vitro and in-vivo studies.

2.1.5.3. Inter-conversion

Relevant for chiral products

2.1.5.4. Pharmacokinetics of metabolites

Pharmacokinetic information available for active metabolites, and if available also inactive metabolites.

2.1.5.5. Consequences of possible genetic polymorphism

Evaluation of consequences if polymorphically expressed enzymes (e.g. CYP2D6, CYP2C19, N-acetyl transference) are involved in the metabolism.

2.1.6. Dose proportionality and time dependency

2.1.6.1. Dose proportionality

Dose proportionality after single dose and at steady state.

2.1.6.2. Time dependency

Systemic exposure after (single and) multiple dose administration of the therapeutic dose and evaluation of time dependency.

2.1.7. Intra- and inter-individual variability

Data on intra- and inter-individual variability in pharmacokinetic parameters, preferably in the target population. If population pharmacokinetic analyses are available, data on intra- and interindividual variability can be taken from these analyses.

2.1.8. Pharmacokinetics in target population

Available PK of parent compound and active metabolites in target population with special emphasis on differences from healthy volunteers including variability in patients. PK population, if available.

Depending on amount of information different sub-headings can be included.

If pharmacokinetics has mainly been documented in the target population and not in healthy volunteers, this section is removed and in the pharmacokinetics in target population is given above.

2.1.9. Special populations

Available PK of parent drug and active metabolites in special populations.

Data from CTD module 5.3.3.3 Intrinsic factor PK study reports and CTD module 5.3.3.5 Population PK study reports (the presentation of data should be similar as in preceding sections and could be included in the single general summary table).

Exploratory analysis of data across studies that may contribute to the understanding of variations in drug pharmacokinetics and possible statements on the consequences may be

displayed here. These variations may be related to extrinsic or intrinsic factors such as age, gender, race, smoking status, metabolic polymorphism, renal function and hepatic insufficiency. Variations related to metabolic polymorphism should be described and assessed under 'Elimination' above. For the paediatric population, modelling and simulation should be included as appropriate.

2.1.9.1. Elderly

Where such data cannot be retrieved from the application dossier or various ages are reported by the applicant, a question table shall be included in the list of questions of the report to be submitted on the 120th day.

Where the disease is prevalent among elderly, specific PK studies in older subjects should be presented or the absence of such studies should be acknowledged.

If PK in older people is likely to be altered, e.g. due to renal impairment, the need for dose adjustment should be discussed.

2.1.9.2. Children

Assessor's overall comments on pharmacokinetics in special populations

Has the pharmacokinetics of parent drug and active metabolites been sufficiently documented in special populations?

Has adequate information regarding pharmacokinetics in special populations and possible lack of information been included in the SPC (restrictions/precautions/dose adjustments)?

It is important to take the PK/PD relationship into account when evaluating the need for restrictions/precautions/dose adjustments in special populations. Both concentration-effect and concentration-side effect relationships should be taken into account.

2.1.10. Interactions

Critical presentation of study results.

Comments on drug-drug interactions should be provided if data are available (the presentation of data should be similar to preceding sections and should preferably be included in a summary table).

2.1.10.1. In vitro

Data from CTD module 5.3.2 in-vitro studies using human biomaterials.

2.1.10.2. In vivo

Data from CTD module 5.3.3.4 Extrinsic factor PK study reports.

2.1.10.3. Assessor's overall comments on interactions

Comments regarding performed interaction studies.

Have appropriate conclusions been drawn from the performed studies?

Discussion concerning the information on interactions included in the SPC (restrictions/precautions/dose adjustments). It is important to take the PK/PD relationship into account when evaluating the need for restrictions/precautions/dose adjustments during concomitant administration of other drugs. Both concentration-effect and concentration-side effect relationships should be taken into account.

Identification of potential interactions, e.g. inhibition or induction of enzymes/transporters that have not been studied in interaction studies in-vitro or in-vivo.

Identification of potential interactions not studied at absorption level.

2.1.11. Exposure relevant for safety evaluation

Summarize the exposure expected in the target population at steady state, and also in specific sub-populations with increased exposure. To be used in preclinical safety evaluation of exposure margins.

2.1.12. Assessor's overall conclusions on pharmacokinetics

The content of this paragraph could be carried forward to the overview assessment report on safety, quality, and efficacy of the assessment.

A self-standing and focused elaboration might therefore be necessary to allow the reader comprehensive access to the relevant findings thus enabling adequate benefit risk assessment.

In this section the assessor should highlight the critical issues, which have been identified in the different sections of the report (absorption, distribution, elimination). Conclude on the quality of the pharmacokinetic documentation with special emphasis on identified deficiencies.

In addition, this section should contain assessment of how the pharmacokinetic information is reflected in the SPC and should especially reflect and substantiate statements made in relevant sections of the SPC. The assessor should discuss whether adequate information and/or precautions/restrictions have been included in the SPC in case of lack of information in certain groups of patients (renal/hepatic impairment, children, elderly etc.).

As an alternative this section could simply state the main conclusions in which case the text in the overview assessment report on safety, quality, and efficacy should be elaborated on separately.

Highlight any areas of agreement/disagreement with the overview assessment report on safety, quality, and efficacy in the submitted dossier.

2.2. Pharmacodynamics

2.2.1. Introduction

Short background on the studies performed; characteristics of healthy volunteers/patients, study design and endpoints.

For similar biological medicinal products the pharmacodynamic effect of the test and the reference products should be compared in a population where the possible differences can best be observed. The design and duration of the studies must be justified. Combined PK / PD studies may provide useful information on the relationship between exposure and effect. The selected dose should be in the steep part of the dose-response curve. Studies at more than one dose level may be useful. If PK/PD studies are used to demonstrate similarity of the biological medicinal products, care should be taken to investigate a reasonable dose range to demonstrate assay sensitivity (see ICH E10 topic). The margins defining equivalence of PK and PD parameters must be defined a priori and justified.

2.2.2. Mechanism of action

The mode of pharmacodynamic action in relation to the clinically desired primary physiological (therapeutic) effects (primary pharmacodynamic action) could be described. The relevance of chosen PD biomarkers could also be discussed here or below.

In addition, taking into consideration the nature of the substance under investigation potential secondary pharmacodynamic actions should be discussed.

2.2.3. Primary pharmacology

The relevance of biomarkers used should be critically assessed.

The mode of action, the dose-response relationship including its time course and the justification for the dose regimen should be further described.

Early dose finding studies are particularly important to describe.

This is aimed at describing the selection of doses for the confirmatory dose-response studies based on parameters of efficacy and tolerability in escalating dosing. The objective is the early understanding of the therapeutic width and to define the dose response of the product.

Describe any genetic difference in PD response as well as potential differences in the paediatric population (e.g. due to maturation).

Results from special studies (e.g. immunogenicity and microbiology) could be described here.

2.2.4. Secondary pharmacology

Consider the secondary pharmacology (as related to the indications). General features of tolerability in healthy volunteers with regard to secondary pharmacology on relevant dynamic endpoint studies, e.g. 24-hour blood pressure, biochemistry, virus levels, ECG, EEG etc.

2.2.5. Relationship between plasma concentration and effect

Data from CTD module 5.3.4 on PK/PD in healthy volunteers and patients.

Relationship between plasma concentration and effect divided into dose response relationships and concentration response relationships with special interest to onset and offset of action.

When available, PK data relevant to PD may also be described here to convey information on sources of variations in PK/PD.

Results on dose/concentration/effect relationship following e.g. population pharmacokinetic screening could also be displayed in section "Clinical Efficacy, dose-response studies" if the results substantiate claims of efficacy and safety.

In principle, exploratory analysis of data across studies that may contribute to the understanding of variations in drug pharmacokinetics/pharmacodynamics may be displayed here or under pharmacokinetics.

The relevance of biomarkers used should be critically assessed.

2.2.8. Assessor's overall conclusion on pharmacodynamics

The content of this paragraph could be carried forward to the overview assessment report on safety, quality, and efficacy of the assessment.

A self-standing and focused elaboration might therefore be necessary to allow the reader comprehensive access to the relevant findings thus enabling adequate benefit risk assessment.

In this section the assessor should highlight the critical issues that have been identified in the different sections of the report and conclude on the quality of the pharmacodynamic documentation with special emphasis on identified deficiencies.

As an alternative, this section could simply state the main conclusions, in which case the text in the overview assessment report on safety, quality, and efficacy should be elaborated on separately.

Highlight any the areas of agreement/disagreement with the "clinical overview" in the submitted dossier and comment on the suitability of the SPC.

3. Clinical efficacy

3.1. General Guidance

The report should be sufficiently detailed to allow for secondary assessment by other assessors of the authorized assessment organization of the reference Member State or Member State concerned.

Although this report should include the necessary details to understand what is in the file you are requested to focus on the salient findings and those deficiencies that justify the questions intended for the applicant with a discussion/interpretation of the results giving the grounds for the benefit-risk assessment and the recommendations of the Expert Committee at the Eurasian Economic Union!

Indiscriminate copying from the applicant's dossier ("Overview" and "Summary") into the AR is not acceptable!

Hence, decide on the minimum detail on individual studies (aim: balanced presentation of "positive" and "negative" findings).

Distinguish (also in comments) between pivotal trials and supportive trials based on judgement on individual importance (mention all studies, if possible, referring to tabulated summaries).

The use of tables/graphs/figures is encouraged (rather than lengthy text!)

There should be a clear separation between data submitted and assessor's comments on that data.

Critical assessment (e.g. comments on the validity and interpretation of the data, conclusions) should be described in the "Assessor's comments" sub-sections that follow each chapter. The words 'Major objection' – see proposed List of Questions, may be used when necessary to cross-refer to the LoQ.

The report should indicate whether additional expertise is needed e.g. a SAG meeting to address some unresolved clinical issues or the need for further assessment of pharmacovigilance issues.

The report should emphasize findings that need to be reflected in the SPC.

3.2. Introduction

Use a brief introductory statement on the general features of the submitted data and the sought indication.

A tabular overview of the relevant clinical studies; study number, design and number of patients in treatment arms, baseline characteristics such as age, gender and severity of disease, efficacy parameters and efficacy results should be included. Such a table should be in accordance with the CTD table 2.7.3.1, as appropriate.

If relevant for the therapeutic indication, describe the experience in special populations to complement what is mentioned under section 3.3.

If applicable, include details about Scientific Advice on Clinical Efficacy (detailed paragraph on advice sought and given).

Include conclusive statement on compliance with GCP, (to be carried forward to 1.2 GCP aspects and the overview assessment report on safety, quality, and efficacy).

3.3. Dose-response studies and main clinical studies

Basis for dose selection for main studies. Details may be given or refer to Clinical Pharmacology.

Brief description (unless elsewhere described) considering, where appropriate, design, size, range of studied doses, justification for surrogate endpoints and results outlining how they have contributed to:

Preliminary evidence of efficacy.

Dose/schedule recommendations.

Include most relevant PK/PD methods and results as well as population PK data and refer to relevant sections for detail.

3.4. Main study(ies)

The methods and results should be presented and discussed as relevant for each of the studies, which should be identifiable in the text (e.g. per protocol number). Tables are encouraged.

A detailed checklist on the description of trial methods, results and discussion is outlined in the template. This extensive checklist is not a requirement; rather, it provides an ordered list of potential items to be included. The relevance of each item and, if appropriate, the required level of detail, needs to be considered on a case-by-case basis.

Critical comments should be included, as appropriate.

Identification and description of the study.

Include the number and title of the study. This should already indicate how participants were allocated to treatment arms (e.g. "random allocation", "randomized", or "randomly assigned").

Note: the Methods or Results can be reported jointly or separately for each trial (depending on the study designs and similarities).

3.4.1. Methods

Keep to most relevant items (see bullets hereafter), on a case-by-case basis.

3.4.1.1. Study Participants

Inclusion/exclusion criteria, locations (e.g., regions where the recruiting sites were located) and settings (type of recruiting sites, e.g. type of hospital/ward) where the data were collected.

3.4.1.2. Treatments

Precise details of treatment (or other type of interventions) intended for each group and how/when they were intended to be administered.

3.4.1.3. Objectives

Specific objectives and hypotheses. State the statistical hypothesis (e.g. superiority, equivalence or non-inferiority for the primary endpoint(s)) and any justification provided for the plausibility of the expected effect size or choice of delta.

3.4.1.4. Outcomes/endpoints

Clearly defined primary and secondary outcome measures and, when applicable, any methods used to enhance the quality of measurements (e.g., multiple observations, training of assessors, central/independent reviews).

If appropriate, focus on the most important secondary endpoints. Describe justifications provided by the applicant to support the validity of any surrogate end-points, if applicable.

Discuss the validity of any surrogate end-points.

Brief comments on the clinical relevance of the aforementioned endpoint(s).

3.4.1.5. Sample size

How sample size was determined and, where applicable, explanation of any interim analyses and stopping rules.

3.4.1.6. Randomization

Methods used to generate the random allocation sequence and stratification criteria to implement it.

3.4.1.7. Blinding (masking)

Whether or not participants, those administering interventions and those assessing outcomes were aware of group assignment and if not, how the success of masking was assessed.

3.4.1.8. Statistical methods

Statistical methods used to compare groups for primary outcome(s) (include definition of the populations for main analysis, error probabilities, adjustment for multiplicity, brief description of the statistical techniques used, interim analyses); methods for additional analyses, such as subgroup analyses and adjusted analyses.

Acceptability of the statistical analysis plan.

Discuss any deviations from the pre-specified statistical analysis plan.

3.4.2. Results

Keep to most relevant items (see bullets hereafter), on a case-by-case basis.

3.4.2.1. Study Participant flow

Describe the flow of the progress of study participants through all the phases of the trial (use of a diagram, as suggested below (or alternatively a table) should be used whenever possible).

Specifically, for each group, report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome, e.g.:

Enrolment (No. subjects screened; No. randomized; No. excluded and reason, dates defining the periods of recruitment).

Allocation (by treatment arm, No. randomized, No. started allocated treatment, No. that did not start allocated treatment and reasons).

Follow-up (by treatment arm, No. lost to follow-up and reasons; No. protocol treatment discontinuation; dates defining the periods of follow-up).

Analysis (No. included into set for analysis of primary endpoint; No. excluded and reasons).

Describe protocol deviations from study as planned, together with reasons.

Describe criteria for treatment rescue and for early escape if relevant for the understanding of the interpretation of the results.

3.4.2.2. Recruitment

Dates defining the periods of recruitment and follow-up.

3.4.2.3. Conduct of the study

State if major amendments were made to the protocol (unless described under statistical analysis). Protocol compliance and GCP inspection findings, if applicable.

3.4.2.4. Baseline data

Baseline demographic and clinical characteristics of each group.

Describe particularly any asymmetry in characteristics across treatment arms.

Discuss how study population reflects intended indication (or defer to overall conclusions).

Discuss similarities and any discrepancies between treatment arms (if applicable).

Discuss treatment compliance, if appropriate.

3.4.2.5. Numbers analyzed

Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention to treat". State results in absolute numbers when feasible (e.g., 10/20 not 50%).

3.4.2.6. Outcomes and estimation

For each primary and secondary outcome, provide a summary of results for each group with estimated precision (e.g. 95% CI).

Clinical relevance of the observed effect should be described since it may be particularly important for the benefit /risk assessment.

3.4.2.7. Ancillary analyses

Address multiplicity by reporting any other analysis performed, including subgroup analyses and adjusted analyses, including prespecified and exploratory ones (subgroup analysis and other post hoc techniques).

Justifications for choice of analysis might be given.

3.4.2.8. Summary of main efficacy results

A tabulated summary of the most relevant information to describe the efficacy data generated in the main trial(s) should be presented. This summary should be tailored to the data set which was used by the CHMP for its conclusion on efficacy. Therefore, it will be important to reflect the results from the analysis that was deemed most relevant (preferably (m)ITT and PP, but maybe also clinically defined sub-group [pre-specified or post-hoc], etc.). The pre-specified primary analysis should be presented in any case.

The following template table should be used to display the data for the specific studies. The level of detail should be adjusted to the data later needed for the discussion and conclusion on benefits, as well as the benefit-risk assessment. Treatment groups should be presented in separate cells, and so should be information on different analysis sets (e.g. ITT and PP). Reasons for drop-outs should be summarized.

Different main trials should be presented in separate tables. No additional text is foreseen in this section apart from these tables. A detailed description of these trials with for instance information on design and power calculation is presented in other sections. The safety data is subject to the section "Clinical safety".

3.5. Clinical studies in special populations

Special studies e.g. in children, in the elderly and in patients with renal or hepatic impairment. Describe these studies as suggested for the main studies including considerations on dose adjustments.

3.6. Analysis performed across trials (pooled analyses AND meta-analysis)

Criteria used for these analyses should be stated and may involve exploratory analysis on the whole database considering different effect modifiers (gender, age, drug-disease interactions, smoking etc.).

In addition dose-effect relationship in special population may need consideration (weight, creatinine clearance etc.).

3.7. Supportive study(ies)

These should be concisely addressed adopting a cumulative approach. For biopharmaceuticals, antibody formation should be mentioned with regard to efficacy (e.g. neutralizing antibodies).

3.8. Assessor's overall conclusions on clinical efficacy

3.8.1. Discussion on clinical efficacy

The discussion is often the most important part of the assessment report. In terms of structure it should in principle follow the flow of the presentation of results above.

Try to be as clear and concise as possible (often discussions are too long and verbose, and the true meaning of the data is not addressed).

For each section, the discussion should address the following points:

Identify the most important findings and deficiencies described above (do not repeat results). Describe how results agree. summarize evidence for each conclusion.

Discuss if the data submitted fulfil the requirements (legal, guidelines, scientific advice)

Describe the major issues raised and to what extent they should be addressed

Highlight important issue that are expected for discussion by the Expert Committee at the Eurasian Economic Union.

Both study design and results should be subject to the critical discussion. Be explicit about the view on key elements like choice of comparators, endpoints as well as shortcoming of the data. The following is a compilation of potential aspects to be addressed in such discussion.

3.8.2. Design and conduct of clinical studies

Was the design of the studies adequate (randomized active and placebo controlled trials)? If not, what are the justifications and are they acceptable?

Was the patient population adequately selected (reflection on inclusion/exclusion criteria)?

Is the comparator considered appropriate? In case of an active comparator, discuss the relevance in view of the Union approved treatment options.

Critical discussion of the appropriateness of the choice of endpoints as well as the duration of the study considering regulatory guidance/scientific advice. Validity of surrogate markers to replace hard endpoints? Acceptability of a composite endpoint and its domains?

Adequacy of the methods, conduct, analysis and reporting of results from main studies, as appropriate. Discuss any particular issues raised regarding the study design.

Is the design in accordance with legal requirements, available guidelines, scientific advice?

What are the implications of any Union GCP inspection?

3.8.3. Efficacy data and additional analyses

Magnitude and clinical relevance of the effect. Clinical relevance of the observed effect should be described since it may be particularly important for the benefit /risk assessment.

What are the key findings (or uncertainties)? What key findings (or uncertainties) should be part of the benefit-risk assessment?

Generalizability (external validity) of trial findings. Do the results support the claimed indication?

Are any additional analyses required and what are the reasons for this request?

If sub-group data is considered of particular relevance for the overall assessment of efficacy, this should be explained.

What major issues were raised during the assessment (major objections and other important concerns)

Discuss any justifications for waiving certain studies or replacing original studies by literature data

Lack of information in certain groups of patients (children, elderly women with childbearing potential etc.) should be mentioned to qualify statement made in section 4.4 of the SPC and it should be mentioned here and summarized in the overall conclusion if follow-up studies have been requested by the authorized assessment organization.

Which are specific considerations for the paediatric population?

For similar biological medicinal products mention explicitly the comparative nature of the results obtained with the chosen reference medicinal product.

How are the findings (or lack of information) reflected in the SPC? Ensure correspondence with SPC (particularly section 5.1) and that all information in the SPC is explicitly assessed and supported by the scientific assessment.

Mention if there are any outstanding data, which remain as post-authorization measures/SO and if this is reflected in the SPC.

3.8.4. Conclusions on clinical efficacy

A brief statement about the conclusions that can be drawn from the clinical efficacy documentation should be provided here.

4. Clinical safety

The safety data should consider the experience available from all patients exposed and therefore should be presented as an integrated analysis. However study-specific features related to clinical safety should be described and the interpretation provided.

Recall concerns identified in non-clinical studies with potential for human use (e.g. toxicity, human metabolites not produced in animals) and in pharmacodynamic studies.

4.1. Introduction

4.1.1. Brief introductory statement on the general features of the submitted data.

For similar biological medicinal products, the clinical safety assessment should highlight any potentially significant clinical differences in terms of the safety profile between the reference and the similar medicinal product.

Special emphasis has to be put on the immunogenicity aspects such as the incidence and characteristics of antibodies. In addition, any consequence for specific post marketing surveillance or pharmacovigilance monitoring should be considered (see Rules of studying biological medicinal products in the Eurasian Economic Union subject to approval by the Eurasian Economic Commission).

4.2. Patient exposure

List clinical studies contributing to safety (summary tables are encouraged)

(Cut-off date should be stated).

Number and characteristics of included patients (age, stage/severity of disease) and healthy subjects, (could be included in the summary table). Size of the database at 6 months and 12 months if appropriate for long-term treatment.

Particularly indicate the safety database for paediatric patients by age groups where appropriate, if applicable.

In general this refers to 6 months and 12 months continuous exposure data, or intermittent exposure.

Any information on exposure >12 months should be provided

Discuss any limitations of the safety database in relation to the proposed target population

4.3. Adverse events

Results should be given by the System Organ Classification (SOC), preferred term including data on severity of all adverse events. A summary table as in CTD (2.7.4.3) is necessary with statistical analyses.

In all cases, the relationship between adverse events and reactions (causality included) and other variables should be addressed.

For example, variables may be:

Duration of treatment.

Dose regimen and schedule.

Cumulative and dose related toxicity.

Co-morbidity and co-medication as appropriate.

Reversibility of the event should be addressed as appropriate. Comment on confirmation of non-clinical findings as appropriate.

Possible relationship with manufacturing/quality issues should be mentioned if relevant (e.g. antigenic compounds).

In case of similar biological medicinal products, even if the efficacy is shown to be comparable, the similar biological medicinal product may exhibit a different safety profile (in terms of nature, seriousness, or incidence of adverse reactions). Pre-licensing safety data should be obtained in a number of patients and for exposure duration sufficient to address the comparability of the adverse effect profiles of the test and the reference product. Care should be given to compare the type, severity and frequency of the common adverse reactions between the similar biological and the reference biological medicinal products.

4.4. Serious adverse events and deaths

Following the overall safety profile, a separate analysis of the serious adverse events and deaths should be made.

Results should be given by the SOC (preferred term) including data on severity of serious adverse events. Summary table as in CTD (2.7.4.3 and 2.7.4.6) is necessary.

In all cases, the relationship between serious adverse events/death, and other variables should be addressed:

For example, variables may be:

Duration of treatment.

Dose regimen and schedule.

Cumulative and dose related toxicity.

Co-morbidity and co-medication as appropriate.

Reversibility / outcome (excluding death) of the event.

4.5. Laboratory findings

Where the disease is prevalent among elderly, safety data in older subjects should be presented or the absence of such studies should be acknowledged

When evaluation elderly data, outcome of assessment of the risk-benefit balance and study size needs to be considered since potential specific risks shall be taken into account (e.g., the impact on cognitive, cardiovascular, renal and hepatic function). When evaluation the risk-benefit balance, the prevalence and severity of comorbidities in the elderly shall be taken into

account, and a polypharmacy shall be assessed, especially when there is an increased possibility of adverse events due to co-administration with other drugs.

A summary adverse events table shall be completed in accordance with the appropriate section of the Appendix 7 to these Rules. Where such a table cannot be drawn up, a question table shall be included in the list of questions of the report to be submitted on the 120th day.

Any claims shown in this section shall be reflected in product information.

Clinically significant deviations (e.g., hemoglobin decreased in 10% of subjects by 2 g/dl over a 20-week exposure) shall be provided (as compared to the data of placebo/active-controlled exposure).

The return to normal levels should be indicated. This information may be included in the table.

Data on subjects who have marked deviations which are 3 times larger than the standard deviation should be reported separately.

4.6. Safety in special populations

Short summary of all available information both derived from preclinical and clinical studies in order to substantiate the specific statements in the SPC (e.g. gender related differences, risks for the use in pregnant women, effect anticipated or observed in children (in the relevant age groups), elderly, etc.).

In general, the wording should be concise and details beyond basic information should only be given when relevant for the critical assessment.

4.7. Immunological events

Antibody formation should be mentioned with regard to safety (e.g. neutralizing antibodies, auto-antibodies, species-specific antibodies, such as HAMA (human anti-mouse antibodies), HAHA (human anti-human antibodies) in the case of monoclonal antibody products. Discuss the validity/usefulness of the assay.

4.8. Safety related to drug-drug interactions and other interactions

Pharmacokinetic and pharmacodynamic interaction-information directly relevant for safety should be mentioned here. Clinical relevant safety experience obtained from other concomitant use should also be considered.

4.9. Discontinuation due to AES

Brief detailing, maybe cross- reference to CTD table (2.7.4.5).

4.10. Post marketing experience

Identify new information obtained from post-marketing experience.

4.11. Assessor's overall conclusions on clinical safety

4.11.1. Discussion on clinical safety

The discussion is often the most important part of the assessment. In terms of structure it should follow the presentation of the results above.

Try to be as clear and concise as possible (often discussions are too long and verbose, and the true meaning of the data is not addressed).

For each section, the discussion should address the following points:

Identify the most import findings and deficiencies described above (do not repeat results). Describe how results agree. Summarize evidence for each conclusion.

State if the data submitted fulfil the requirements

Describe the major issues raised during the assessment (major objections and other important concerns) and to what extent they should be addressed

Highlight important issue that are expected for discussion by the extended board of assessors of the assessment organization of the Member State.

Conclude and state what information should be reflected in the SPC and the opinion

What key findings (or uncertainties) should be part of the benefit-risk assessment?

4.11.1.1. Specific points for discussion

Patient exposure: Discuss any limitations of the safety database in relation to the proposed target population.

How are the findings (or lack of information) reflected in the SPC? Ensure correspondence with SPC (e.g., Sections 4.3, contraindications, 4.4 special warnings, 4.7 Effects on ability to drive and use machines 4.8 Undesirable effects, 4.9 Overdose, as appropriate) and that all information in the SPC is explicitly assessed and supported by the scientific assessment.

Description of the safety profile of the medicinal product and degree of safety assessed

Is the safety profile in accordance with that expected from nonclinical studies and known class effects?

Describe relevant safety aspects specific for the paediatric population by age group where appropriate. Link this closely to the recommendations in the SPC. Are there any specific (serious) ADRs and/or monitoring requirements?

Sufficient long-term data? Mention if there are any outstanding data which remain as post-authorization measures and if this is reflected in the SPC. Additional post-marketing studies/follow-up measure (FUM)?

For similar biological medicinal products mention explicitly the comparative nature of the results obtained with the chosen reference medicinal product.

4.11.2. Conclusions on clinical safety

A brief statement about the conclusions that can be drawn from the clinical safety documentation should be provided here (e.g., most frequent adverse drug reactions and other significant safety issues).

5. Pharmacovigilance

5.1. Pharmacovigilance system

Note that the future MAH must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market and for as long as the marketed product remains in use.

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided.

5.1.1. Key issues for consideration by the assessor:

Have the various elements set out in the guideline been provided, if not is any omission justified? Are missing elements or elements stated as intentions, (that will be put in place before putting the product on the market) adequately addressed and to be included in FUMs – are these commitments realistic and credible).

Is this the first product that this company will place on the market, and how prepared do they appear to be? If it is not the first product, is there a history of compliance issues from the assessment of ICSRs or PSURs of the other products – in other words does the system of this company appear to give problems?

Is there a previous Phv inspection history, in particular a negative one, or no previous inspection (this will be the case often in the near future but should be less so as time goes on?

Does the system described appear to be able to deal with what may be the anticipated volume of safety reports for this product, or does it appear “too small” to deal with them? Does the product have a much higher risk-benefit ratio than previous products of the MAH?

Is there a complex array of subcontractors and licensing partners etc., i.e. a system with many organizational interfaces – these are often the weakest points?

Has the company recently merged?

Are the arrangements very specific to the product (which means they are perhaps not tried and tested, even if they are apparently well established companies/subcontractors)?

Is this the description of an existing system or is it mainly an intention to put in place if the product is authorized? – this will be most likely for first products, or very new and different licensing arrangements.

Does the description represent a major change to their existing system?

Is the QP role subcontracted? If so does it appear that they have influence on the pharmacovigilance system?

Is there other information that gives rise to concern about the likely compliance of the system described (e.g. information from other authorities, known problems with respect to a particular contractor, software…)?

Is a Phv inspection, soon after the product is placed on the market, recommended because of some of these issues?

Other issues that may arise

Consider the following statements in the AR:

<The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Member States or in a third country has been provided.>

<The assessor considers that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Member States or in a third country.>

If on the other hand there are outstanding items to be resolved in the pharmacovigilance system description and implemented before the medicinal product is put on the market, should be listed as questions in the LoQ and/or ultimately as FUMs in the final overview assessment report on safety, quality, and efficacy. If deficiencies have been identified with the description of the pharmacovigilance system or the availability of the QP and means to report adverse reactions, one of the following paragraphs should be stated depending upon the severity of the deficiencies.

<The assessor considers that the Pharmacovigilance system as described by the applicant has the following deficiencies:<list the deficiencies>

<Provided that the deficiencies are rectified prior to the applicant placing the medicinal product on the market, the assessment organization may consider that the Pharmacovigilance system will fulfil the requirements. The applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market>

5.2. Risk management plan

At Day 80 the assessor should have performed the first overall assessment of the application, together with identification of any major issues in the RMP. To assist the pharmacovigilance assessor in the provision of their advice it would be helpful for the assessors to flag to the overview assessment report on safety, quality, and efficacy any particular issues and concerns that were identified during the assessment of the dossier that could impact the Risk Management Plan. This includes any particular nonclinical safety findings, gaps in the clinical pharmacology package, potential safety signals from the clinical trials, etc. At this stage it is particularly important that safety concerns are identified (important identified risks, important potential risks, important missing information). This is even more essential if these issues were not identified by the applicant in the dossier and are therefore unlikely to be reflected in the RMP.

Once the Advice is received, this will be integrated into the draft List of Questions for discussion. It is important to note that this Advice may also contain proposed questions on the Risk Management Plan to be added to the List of Questions.

Questions and issues shall be listed based on the outcome of the assessment and which shall be discussed during RMP evaluation.

6. List of references

7. List of questions as proposed by the assessor

7.1. Definitions of questions:

"Major objections", preclude a recommendation for marketing authorization. In principle, one major objection may entail more than one question and the use of bullet points or subheadings is encouraged. It is vital that the structure and content of a major objection are clear and understandable to the reader. Detailed comments may be necessary along with a reference to guidance documents. Ideally, the objection should include a clarification as to what kind of response/action is expected from the applicant.

"Other concerns", may affect the proposed conditions for marketing authorization and product information. For example, if there are no data in renally impaired patients, new data may resolve this question whereas lack of such data may lead to amendments in the SPC/post-authorization measures. Other concerns should be resolved before approval: failure to do so may render the application un-approvable.

Comments should be made on the need for paediatric development in relation to questions on the clinical development

This list should be carried forward to the overview assessment report on safety, quality, and efficacy.

'Recommendations' shall contain assessor's comments/conditions which do not preclude granting a marketing authorization and which might be resolved having the marketing authorization been granted using variation to a MAA procedure.

8. Recommended conditions for marketing authorization and product information

Points relating to this heading should also be specifically addressed in the relevant section of the overview assessment report on safety, quality, and efficacy, (e.g. specific comments on the product information).

User Consultation' of the package leaflet

The applicant has to provide results of assessments carried out in cooperation with target patient groups on the package leaflet ('user consultation') or a justification for not performing such consultation. Please refer to the relevant Union guidance documents for more information on the requirements, presentation and assessment of the 'user consultation' results:

In all cases, it should be assessed and stated (see the "overview") whether 'user consultation' of the PL has been performed or is foreseen, or whether the justification for its absence is acceptable.

In case a 'user consultation' of the PL has been performed and is included in the application, the assessor shall include the assessment of the results of 'user consultation' in their assessment reports, as well as a conclusion on the overall readability of the PL.

More general comments could also be made here.

APPENDIX 16
to the Rules of authorization
and assessment of medicinal products
for human use

OVERVIEW TEMPLATE

(template)

Critical assessment report on Safety, Efficacy, and Quality

OVERVIEW

[Trade name]

_____

(Active substance)

_____

Application No. _____Dated _____

Applicant _____

Report dated _____

TITLE PAGE

Brand name of the medicinal product in the reference Member State	
INN (or common name) of the active substance(s)	
Pharmaco-therapeutic group (ATC code)	
Pharmaceutical form(s) and strength(s)	
Application number:	
Reference Member State	
Member States concerned	
Name of the marketing authorization holder and its address in the Member States concerned	
Name and address of the manufacturer(s) of the finished medicinal product Name and address of the manufacturer(s) responsible for batch release within the Eurasian Economic Union	
Date of the first marketing authorization	
Marketing authorization certificate number in the Member State concerned	
Contact person in the Member State concerned	Full Name Tel.: E-mail:
Names of the assessors	Quality: Name Tel: Email: Nonclinical: Name Tel: Email: Clinical: Name Tel: Email:

I. RECOMMENDATION

Based on the review of the data on quality, safety and efficacy, the Member State concerned considers that the application for <*medicinal product name*> in the treatment of <*claimed indication*>. Marketing authorization in the country issued on <*date*>.

II. EXECUTIVE SUMMARY

II.1. Problem statement

Product justification: epidemiology, basic characteristics of the disease and the current therapy.

Note: This section is not applicable in respect of applications for generic drugs.

II.2. About the medicinal product

Mechanism of action.

Pharmacological classification.

Claimed indications and recommendations for use (including a possible risk management strategy) and posology.

Special pharmaceutical aspects, if any, e.g. novel delivery system etc.

II.3. General comments on application dossier

Indicate type of marketing authorization application (reference to the legal basis of the application).

Clarify the key aspects of the dossier, if appropriate.

Specify whether an active substance is qualified as a new active substance.

For applications filed under Sections 14.4 and 15.2 of Appendix 1 to the to the Rules of authorization and assessment of medicinal products for human use of the Eurasian Economic Union (simplified dossier), in this section, a document of Module 1.5.1 summarizing any reasons and data used to demonstrate that the use of the substances included in a medicinal product is well established and has an acceptable level of safety and proven efficacy shall be submitted. A robust scientific justification shall be given for omission of any studies which are usually conducted in own country.

For generic applications: in this section, a document of Module 1.5.2 summarizing the facts and reasons showing that the product is almost equivalent to the original product.

Indicate whether the applicant has submitted a Risk Management Plan, where applicable.

Introduce and comment the clinical development program in view of the proposed indication and posology, where applicable.

State if, and when scientific advice was given and indicate whether the advice was followed by the applicant.

Indicate availability and need for development in paediatric population and in other special populations such as the elderly, male/female and ethnic minorities.

II.4. General comments on compliance with GMP, GLP, GCP and agreed ethical principles

<The Member State concerned has confirmed compliance with the requirement of the Good Manufacturing Practice (GMP) in respect of all medicinal product manufacturing and packaging sites, <except for ... It is necessary to carry out an inspection of the site, because ... ...>

<For manufacturing sites within the territory of ... Member States concerned, copies of valid manufacturing authorizations issued by the competent inspection authorities as a proof of compliance of these sites with GMP.>

<For manufacturing sites... copies of the current GMP certificates have been accepted based on the satisfactory inspection reports, letters on the elimination of non-compliance after corrective actions, or the exchange of information sent by the competent inspection authorities (or those countries with which the Union has concluded an agreement on mutual recognition) as a proof of compliance of these sites with GMP.>

Elaborate as appropriate in concordance with points made in the critical assessment modules.

A specific comment should be made as to whether any inspections are needed and if so whether it is GMP, GLP and/or GCP.

Where it is considered that one or more inspections are required make a cross-reference to the detail in sections on GMP, GLP, or GCP in the related Quality, Non Clinical, or Clinical reports.

The inspection request should be referenced in the relevant part of sections III and VI of this document.

III. SCIENTIFIC OVERVIEW AND DISCUSSION

In this section, information from the "Critical assessment reports ..." as provided in Appendices 6 to 8 may be used. The relevant wordings are given in the end of the relevant parts of Appendices 6 to 8. The assessor may on its own copy and paste in these wordings under the relevant headings below.

Although this report shall include the necessary details to understand what is in the file you are requested to focus on the salient findings from each part of the critical assessments with a discussion/interpretation of the results giving the grounds for the benefit-risk assessment and the Member State concerned recommendations and the questions posed to the applicant.

For generic applications:

If a reference product is used, then the state of reference should clearly indicate whether the rationale for the use of the drug is based on its own materials or data provided on request by another Member State of the Union (hereinafter referred to as a member state).

If the general characteristics of the generic drug differ from the summary characteristics of the original product, the evaluation report must contain data justifying the changes in question.

If the summary of product characteristics for the generic medicinal product differs from that of original product, the assessment report shall contain a justification for such changes.

III.1. Quality aspects

Active substance

<The chemical and pharmaceutical documentation and general summary of quality with respect to <name of product> are of acceptable quality in terms of the existing regulatory requirements.>

<Control tests and specifications for the active substance have been properly performed.>

<Regarding the drug, stability tests have been conducted. No significant changes in any parameters have been identified. The proposed retest period is <...> and justified.>

Medicinal product

<Development of the finished product has been described, the choice of excipients is justified and their functions have been explained.>

<The specifications for the finished product include appropriate parameters for this dosage form. Validation of analytical procedures is presented. The batch analysis was conducted on the series <number>. According to the batch analysis, finished products comply with the proposed specifications.>

<The conditions of the stability tests comply with the rules for conducting stability tests of the International Conference on Harmonization (ICH). Control tests and specifications for the active substance have been properly performed.>

<The proposed shelf life of <number> months at <specify the storage conditions> for the finished product is acceptable.>

Specify what is expedient in accordance with the provisions of the preliminary assessment modules.

The following information may be added:

- General information about the results of the dissolution test;
- A statement that the active ingredients and excipients used are well known and are of proper pharmacopeial quality;
- Statement about an active substance stability certificate issued by the European Directorate for the Quality of Medicines (EDQM).

III.2. Non-clinical aspects

In an application on generics, it is usually a matter of known substances. During the nonclinical evaluation one should focus on new information. It is only permitted not to carry out nonclinical evaluation in cases where the drug can be classified as well-studied in both the reference Member State and the Member State concerned, as well as in the absence of new data on the results of nonclinical studies. However, if new nonclinical research data emerges (for example, in relation to pregnancy and lactation, the QT interval, etc.) that could affect the SmPC, a new nonclinical evaluation should be carried out.

"Bibliographic" statements are applications of "an incomplete dossier." Here it is necessary to consider data from nonclinical studies. The evaluation report must specify whether the submitted study (literary publication) has significance for the drug. If some studies have not been conducted, it is necessary to give a clear scientific justification for rejection of such research on the basis of the criteria of "well established medicinal use" permitted under Appendix 1.

Pharmacology
Pharmacokinetics
Toxicology

III.3. Clinical aspects

Generic applications:

For medicinal products with systemic action this section should highlight the need to conduct bioequivalence studies or show that such research is not significant or necessary. Here it is necessary to generalize the conclusion of the evaluation of these studies;

In a confidential annex (not to be disclosed to the applicant) it is necessary to specify the full content and specification of the reference product used in the bioequivalence studies so that the Member States concerned can compare it with data on drugs allowed for sale within their territory.

It is necessary to provide justification for the use of the reference drug.

If the SmPC differs from the original drug used for comparison, the assessment report shall contain information justifying the appropriate changes.

"Bibliographic" applications are applications of "an incomplete dossier." Here it is necessary to consider the data of clinical studies.

Pharmacokinetics
Pharmacodynamics
Clinical efficacy
Clinical safety
Pharmacovigilance system

<The applicant (prospective future marketing authorization holder) submitted a signed explanatory note for the applicant's (the proposed future marketing authorization holder's) pharmacovigilance system (type IA/<X> change). The reference state considers the explanatory note acceptable, subject to full compliance of the pharmacovigilance system dossier with the requirements of the module on good pharmacovigilance practice.>

Risk management plan

Insert the summary table(s) of the proposed activities in the field of pharmacovigilance and minimization of risks from hazards.

<Risk Management Plan is approved>

If the risk management plan is presented in the format previously used, it must be presented in a new format along with data on adverse drug reactions as of day 60 of the procedure.

Periodic safety update report on the medicinal product

<The marketing authorization holder shall submit the first periodic safety update reports for this product within {xx} months after its registration. Subsequently, the holder of the registration certificate shall submit periodic safety update reports for this product.>

IV. ASSESSMENT OF THE BENEFIT-RISK BALANCE

Summarize the main conclusions and questions for the evaluation (detailed information must be given in the main sections on quality, efficacy and safety, respectively). Integrate these aspects when considering the benefit-risk ratio for certain populations.

Include data on nonclinical and clinical safety and commitments in the post-registration period after registration, and consider all aspects of risk management that could affect the assessment of the benefit-risk ratio.

The assessment of the benefit-risk ratio must also include the following aspects, if applicable (taken from the registration dossier in the common technical document format):

1. Compliance with the requirements of the governing documents of the Eurasian Economic Commission and the Expert Committee of the Eurasian Economic Commission.
2. The optimum dose range and posology.
3. Efficacy and safety in sub-populations (e.g., subjects of a certain age, gender, race, extent of

organ function, the severity of the disease and genetic polymorphism).
4. Known and potential mechanisms of drug-drug interactions.
5. Safety "signals" related to carcinogenic or teratogenic effect, prolongation of the QT interval or suspicion of hepatotoxicity.
6. Using surrogate endpoints for effective action when toxicity is serious.
7. Checking consideration of all safety issues in terms of pharmacovigilance (if present).
8. Safe and/or effective use of the drug assumes potential difficulties in the choice of management approaches requiring special medical expertise or subject education.
9. Checking the recording of the risks and uncertainties in the conditions of the issuance of the marketing authorization as part of the information about the drug, follow-up inspection activities, or the risk management plan.
10. Check for sufficient information to characterize the benefit-risk ratio of the drug, compared with the proper recognized treatment scheme (if any). To be considered in the respective order.

In addition, it is necessary to consider data on children or any development plans for pediatric use.

If it is appropriate, this section should include information and data from bioequivalence assessment for applications for generics. It is necessary to highlight the choice of the reference drug.

V. RECOMMENDED CONDITIONS FOR MARKETING AUTHORIZATION AND PRODUCT INFORMATION

V.1. Conditions for the marketing authorization

Legal status

The conclusion of the reference state on the proposed procedure for dispensation of the drug is necessary.

Subsequent control measures

Special commitments
In this section, the conditions for the issuance of the marketing authorization must be specified (if applicable):

V.2. Summary of product characteristics
V.3. Leaflet and user consultation
V.3.1. Leaflet
V.3.2. Evaluation of user consultation

In the state of reference it is necessary to include an assessment of user testing (if any) using the appropriate annex to the Requirements for the instructions on medical use of drugs and the summary of product characteristics and a check-list for the analysis of the results of user testing. Otherwise, you must specify whether user testing is provided for or justify the acceptability of its absence.

<Evaluation of user testing is shown in the attached instructions for checking the quality of documentation and the check-list for the analysis of the results of user testing.> or <The commitment of the applicant to carry out a test on the readability of instructions for medical use during the period of suspension of the marketing authorization may be approved.

V.4. Labeling

VI. ANNEX. QRD GUIDANCE AND CHECKLIST FOR THE REVIEW OF USER TESTING RESULTS

This guidance has been developed to provide practical information on how to evaluate user testing reports which are based on the readability testing method. This does not exclude the submission and evaluation of user testing reports based on other methods than the one outlined above.

PRODUCT INFORMATION

Name of the medicinal product	
Name and address of the applicant	
Name of the company which has performed the user testing	
Type of Marketing Authorization Application	
INN	
Pharmacotherapeutic group (ATC Code)	
Therapeutic indications	

Full user testing report provided ☐ Yes ☐ No

Summary report provided ☐ Yes ☐ No

In the case of a summary report, multiple supporting studies are inadmissible in principle.

However, for one drug 3 supporting studies are allowed (e.g., one on the scientific content, a second on the device and the last on the leaflet layout).

Grounds for bridging testing based on a sound justification:

☐ extensions for the same route of administration

☐ ref to test on same class of medicinal product

☐ ref to test with same safety issues

☐ other (specify): _____

Is the justification for bridging acceptable? (If no user testing report or summary report has been provided, a justification should be given). ☐ Yes ☐ No

Is the justification for not submitting a report acceptable? (Examples of grounds that are not considered an acceptable justification for the lack of user testing are listed below: ☐ Yes ☐ No

Administration in a hospital setting only;

Administration by a healthcare professional only;

Compliance with the QRD templates;

Long established use of the product.

Reasons *[assessor's views on acceptability or not of the justification for not submitting user testing report or bridging form]*

_____

_____

_____

_____

1. Technical assessment

1.1. Recruitment

Is the interviewed population acceptable? ☐ Yes ☐ No

Comments/further details_____

Guidance regarding Recruitment

The following points should be taken into consideration when assessing recruitment methods:

Is the recruitment method well defined? Is it clear that serious thought was given to the composition of the test group? (e.g. in terms of variables such as sex, age, education, previous job titles (in case of retirement, change of employment), job description and professional experience (e.g. vocational training, complete qualifications, use of information technology) in order to assess their level of education, experience with the medicinal product, existing knowledge of the complaint, etc.)?

Is a listing of any respondents who volunteered previously in user testing and how often they have done so available?

Is it clear how many people were involved in the test/test rounds?

Is that number sufficient? (The PL should be tested in minimum 2 rounds of 10 participants each).

1.2. Questionnaire

Is the number of questions _____ sufficient? ☐ Yes ☐ No

Questions cover significant (safety) issues for the PL concerned? ☐ Yes ☐ No

Comments/further details_____

Guidance regarding Questionnaire

The following points should be taken into consideration when assessing the questionnaire:

Has the applicant provided basic information on safe administration?

Do the questions cover the key messages and the following areas?

=>General impressions of package leaflet;

=>"Diagnostic" part of PL (i.e. questions aiming to test whether the participants were able to find specific information quickly and easily in each section of the PL and to verify if they were able to understand this information correctly; the questionnaire should primarily concentrate on safety and correct use of the medicinal product and understanding of the participant to assure safe use –it must be ensured that key safety messages have been addressed);

=>"Aspects such as design and layout of PL;

Is the number of questions sufficient? (too few or too many – e.g. 12-15);

Do the questions address "wording" aspects? Can respondents easily understand the text they are reading?

Do the questions provide open or pre-defined answers? Respondents should not be provided with ready-made answers which would increase the possibility of positive results. They should instead answer in their own words in order to check if they understand the information correctly. Questions should be open, should be ordered randomly to see how patients use the PL and should not be leading (however, it is good practice to start with an easy question to ease the participant). Questions that require self-assessment (example: in your opinion, is paragraph X clear?) should not be used. Questions that require a long list of answers to be given (example: "what are the adverse events of this medicinal product?") should also not be used..

1.3. Time aspects

Is the time given to answer acceptable? ☐ Yes ☐ No

Is the length of interview acceptable? ☐ Yes ☐ No

Comments/further details_____

Guidance regarding Time aspects

The following points should be taken into consideration when assessing the time aspects:

Is it clear how long the test lasted?

Was the time given for respondents to read and answer the questions adequate? How long did the interview last? [The test should be designed in a way to last no more than 45 minutes, to avoid tiring participants]

1.4. Procedural aspects

Rounds of testing including pilot_____

Comments/further details_____

Guidance regarding Procedural aspects

The following points should be taken into consideration when assessing the procedural aspects:

Is the test based on different testing rounds? (a minimum of two test rounds, each involving 10 participants, is required: As this is an iterative process more rounds may be required in order to satisfy the success criteria; a pilot test (including 2 to 3 persons) could precede to assure the questionnaire is understood and major gaps are precluded. The PL after changes should then be tested on 20 participants in total. However, one single testing round may also be considered sufficient and acceptable on a case-by-case basis)

A satisfactory test outcome for the method outlined above is when 90% of literate adults are able to find the information requested within the PL, of whom 90% can show they understand it, i.e. each and every question must be answered correctly by at least 81% of the participants.

Does it makes use of modification phases in-between the testing rounds in order to maximise readability?

Do interviewers use scenarios or live demonstrations (e.g. in order to increase the efficiency of the test, if appropriate?

1.5. Interview aspects

Was the interview conducted in well structured/organised manner? ☐ Yes ☐ No

Comments/further details_____

Guidance regarding Interview aspects

The following points should be taken into consideration when assessing the interview aspects:

Are there clear instructions for the test instructor(s)? (e.g. instructions on how to get more information from the consumers test, whether or not help should be given, etc.)?

Do interviewers let respondents show where information on the medicinal product can be found in the leaflet?

Do they ask respondents to give their answer in their own words and not to rely on memory?

2. Evaluation of responses

2.1. Evaluation system

Is the qualitative evaluation of responses acceptable? ☐ Yes ☐ No

Does the evaluation methodology satisfy the minimum prerequisites? ☐ Yes ☐ No

Comments/further details_____

Guidance regarding Evaluation system

The following points should be taken into consideration when assessing the evaluation system:

Is the assessment based on a check list covering the following 3 basic areas:

⇒To find the information (e.g. can a respondent easily find the information on dosage?);

⇒ To understand the information (e.g. can a respondent say in his/her own words what the proper dosage and the instructions for use are?);

⇒ To use the information (e.g. "imagine you are in situation X and Y happens, what must you do?").

2.2. Question rating system

Is the quantitative evaluation of responses acceptable? ☐ Yes ☐ No

Comments/further details_____

Guidance regarding Questions rating system

The following points should be taken into consideration when assessing the questions rating system:

How are answers evaluated? (e.g. 1= no answer, 2=wrong answer, 3=incomplete answer, 4=ambiguous answer, 5=complete and correct answer).

3. Data processing

Are data well recorded and documented? ☐ Yes ☐ No

Comments/further details_____

Guidance regarding Data processing

The following points should be taken into consideration when assessing the data processing:

Is it clear how the data are recorded?

Is the way in which they are recorded satisfactory?

Have the data been processed satisfactorily? (e.g., is it clear how verbal assessments have been converted into graded answers?)

Has the assessor been provided with the patient leaflets used during (different rounds of) testing?

Are the revisions in the PL explained/justified? Is it also clear which comment from the participants were ignored and why?

4. Quality Aspects

4.1. Evaluation of diagnostic questions

Does the methodology follow the Requirements for the medication guide (patient leaflet) and summary of product characteristics of medicinal products for human use? ☐ Yes ☐ No

Overall, each and every question meets criterion of 81% correct answers? ☐ Yes ☐ No

Comments/further details_____

4.2. Evaluation of the layout and design

Follows general design principles of the Requirements for the medication guide (patient leaflet) and summary of product characteristics of medicinal products for human use? ☐ Yes ☐ No

Language includes patient friendly descriptions ☐ Yes ☐ No

Layout navigable ☐ Yes ☐ No

Use of diagrams acceptable ☐ Yes ☐ No

Comments/further details_____

Guidance regarding Quality aspects

The following points should be taken into consideration when assessing the quality aspects:

Is the report complete?

Does the report clearly distinguish between quantitative and qualitative results?

Is the medicinal product and the company concerned clearly indicated?

Based on EAEU guidelines, are "diagnostic" questions (see 1.2) scoring satisfactorily?

Do respondents find the layout and design of the package leaflet satisfactory?

Special focus should be given to the following elements:

Writing style (simple language, short sentences, use of bullets)

Type face (font size, italics/underlining, lower/upper case)

Layout (spacing, white space, contrast, left justified, columns)

Headings (consistent location, stand out)

Use of color (present, adequate contrast)

Pictograms should be subject to user testing as it is well known that these can confuse patients.

Do respondents encounter difficulties in locating and using correctly (if appropriate) the information provided in the PL?

5. Diagnostic quality/evaluation

Have any weaknesses of the PL been identified? ☐ Yes ☐ No

Have these weaknesses been addressed in the appropriate way? ☐ Yes ☐ No

Comments/further details_____

Guidance regarding Diagnostic quality/evaluation

The following points should be taken into consideration when assessing diagnostic quality/evaluation:

Are the results (as far as possible) related to actual passages of text?

Is an attempt made to explain that readers' problems arose because of certain characteristics of those passages (e.g. something was difficult to find because of a badly chosen heading; or a passage could not be understood because of a double negative; or specific information could not be applied properly because certain terms were unclear)?

Was a second round revision carried out?

Have weaknesses of the first round been clearly identified and addressed in the appropriate way? (e.g. questions that scored low led to modifications on the PL => introduction of stylistic changes to improve readability or removal of redundant and confusing information)

Is it clear which passages have been revised and how and on the grounds of what observations in the first round?

Is it also clear what observations were ignored in making the revision and why?

Have modifications been tested and proved to improve readability?

6. Conclusion

Have the main objectives of the user testing been achieved? ☐ Yes ☐ No

Is the conclusion of applicant accurate? ☐ Yes ☐ No

Overall impression of methodology ☐ Positive

☐ Negative

Overall impressions of the patient information leaflet structure ☐ Positive

☐ Negative

CONCLUSION (SUMMARY)_____

_____

_____

Guidance regarding Conclusions

A general view on the user testing performed and on the overall readability /quality of the PL should be provided here *[the complete evaluation report of the user testing results should only be included as an Annex of the assessment report]*

The following points should be taken into consideration when drafting the conclusions:

Objectives:

To ensure the final PL reflects the results of testing with patients to make sure it meets their needs and can enable the patient to use the medicinal product safely and effectively;

To assess the readability of the PL

To identify problems regarding comprehensibility and usefulness of information

To describe possible changes in the leaflet in order to improve the readability of the leaflet.

Does the report make it clear on what test results specific conclusions are based?

Do the conclusions match the results or, given the actual results, is too favorable a picture painted?

Are the conclusions clear, concise and well organized?

Have the recommendations and conclusions also been incorporated in any revision of the text?

APPENDIX 17
to the Rules of authorization
and assessment of medicinal products
for human use

TEMPLATE
Certificate of marketing authorization for a medicinal product for human use

(template)

CERTIFICATE OF MARKETING AUTHORIZATION

for a medicinal product for human use

MP-№ (XXXXXX)-(YY-ZZ)

_____

(certificate of marketing authorization number)

In accordance with the Rules of authorization and assessment of medicinal products for human use, this certificate of marketing authorization is hereby issued to:

1	Name of the marketing authorization holder:	
2	Address of the marketing authorization holder:	
3	Date the marketing authorization granted:	
4	Period of validity of the marketing authorization:	
5	Date of renewal of the marketing authorization:	
6	Date the certificate amended (re-issued):	
7	Date the marketing authorization granted in the reference Member State:	

and confirms that the medicinal product has been authorized and approved for medical use within the territory of

_____

(Eurasian Economic Union Member State)

Information about the authorized medicinal product

8	Brand name of the medicinal product:	
9	International Non-proprietary Name (INN) or common name or chemical name of active substance (where no INN exists):	

10	Dosage form:	
11	Strength(s):	
12	Presentation(s):	
13	Composition of the finished medicinal product:	

Finished medicinal product manufacturer's details
(names and addresses of manufacturing sites
involved in the manufacturing process of finished medicinal product)

№	Manufacturing step (all stages)	Company name	Manufacturing site address
1	Manufacturing of the finished medicinal product		
2	Primary packaging (filling)		
3	Secondary packaging		
4	Batch release		

__-page Annex.

Head of the competent authority Signature SEAL

(or authorized person)

TEMPLATE for Annex
to Certificate of marketing authorization
for a medicinal product for human use

Annex No ___
to Certificate of marketing authorization
for a medicinal product for human use

No _____

SPECIFIC CONDITIONS OF THE MARKETING AUTHORIZATION

Restrictions regarding medicinal product use imposed in the course of granting the marketing authorization

Marketing authorization holder's obligations to be fulfilled as conditions of marketing authorization

Deadline for fulfilling obligations and restrictions imposed in the course of granting the marketing authorization on the marketing authorization holder

Head of the competent authority Signature SEAL

(or authorized person)

RULES
of completing of a certificate of marketing authorization for a medicinal product for human use

1. Certificate of marketing authorization for a medicinal product means a document which confirms the authorization of the medicinal product within the Eurasian Economic Union (hereinafter referred to as the Certificate and Union, respectively) and which is competed by the competent authority of the Union Member State granting marketing authorizations for medicinal product within the Union (hereinafter referred to as the competent authority and Member State, respectively), in accordance with these Rules using a single template.

2. Certificate shall be completed in Russian using printing devices and where an appropriate requirement is envisaged in the Member State legislation using official language of the Member State to which issuing competent authority belongs. Where the documents to be issued in Russian and official language of a Member State, these shall be completed using two-sided templates where each side corresponds to the appropriate language.

The Certificate is a document of strict accountability; the template shall be printed and have security measures in accordance with the relevant Member State legislation.

Where necessary, the manufacturer's name, its address (legal address), name and address of the marketing authorization holder may be printed (added) using Latin alphabet.

3. The following convention shall be used for the certificate number:

MP-№(XXXXXX)-(YY-ZZ) где:

'MP' is medicinal product;

'№(XXXXXX)' is a single 6-digit certificate serial number assigned by the reference Member State which to be assigned automatically by the Common Register of the Authorized Medicinal Products within the Union.

'YY' indicates the status of the Member State within the assessment and granting a marketing authorization; RMS means reference Member State, CMS means Member State concerned.

'ZZ' is the 2-letter country code of the Member State in accordance with the ISO 3166-1-2013 standard *Codes for the representation of names of countries and their subdivisions*—Part 1: Country codes: The Republic of Armenia—AM; Belarus—BY; The Republic of Kazakhstan—KZ; Kyrgyz Republic—KG; Russian Federation—RU.

4. Section 1 shall contain the name of the marketing authorization holder.

5. Section 2 shall contain the address of the marketing authorization holder, including the country.

6. Section 3 shall contain the date the marketing authorization was granted in DD.MM.YYYY format; this date indicates when the competent authority made the decision granting the marketing authorization for a medicinal product.

7. Section 4 shall contain the period of validity of the marketing authorization in DD.MM.YYYY format; this period shall be counted beginning with the date the marketing authorization was granted.

8. Section 5 shall contain the date of renewal of the marketing authorization in DD.MM.YYYY format; this period shall be counted beginning with the date the marketing authorization was granted by the reference Member State.

9. Section 6 shall contain the date the certificate amended (re-issued) in DD.MM.YYYY format.

10. Section 7 shall contain the date the marketing authorization was granted in the reference Member State.

11. The Member State name which allowed medical use of the medicinal product within its territory shall appear in the rows under the table.

12. Section 8 shall contain the Brand name of the medicinal product in accordance with the Requirements for the medication guide and summary of product characteristics of medicinal products for human use subject to approval by the Eurasian Economic Commission.

13. Section 9 shall contain the International Non-proprietary Name (INN) of the active substance; where no INN exists, the common name shall be used; where neither exists, chemical name in accordance with IUPAC nomenclature shall be used. For combination medicinal products, the appropriate common name shall be used; this name shall be a list of INN and/or common names connected with '+' mark in alphabetical order. Where pharmacological action of one or more active ingredients do not directly furnish the pharmacological effect of the medicinal product being supplementary, the name of such ingredient(s) shall appear in square brackets at the end of the common name regardless of alphabetical order.

14. Section 10 shall contain the pharmaceutical form name in accordance with the Nomenclature of pharmaceutical dose forms of the Union; for kits the name of pharmaceutical form of each kit component shall be provided.

15. Section 11 shall contain the description of the strength of each dosage unit. For combination medicinal products, the strength of each strength of each dosage unit shall be separated by '+' mark and in order which correspond to the appropriate common name. Strength declaration shall be identical to the information in the normative document of medicinal product.

16. Section 12 shall contain the description of the medicinal product presentation including the inner packaging and the outer packaging together with the pack size together with any other component of the product. The information shall be identical to the information in the normative document of medicinal product.

17. Section 13 shall contain the description quantitative composition of active substances and qualitative composition of excipients of the medicinal product. The information shall be identical to the information in the normative document of medicinal product.

18. Section 14 shall contain the shelf life of the medicinal product using the appropriate period term such as 1 year, 2 years, 3 years, etc. The shelf life shall be identical to the information in the normative document of medicinal product.

19. The Table *Finished medicinal product manufacturer's details (names and addresses of manufacturing sites involved in the manufacturing process of finished medicinal product)* shall be completed with addresses of all manufacturing sites as laid down in 3.2.P.3 *Manufacture of the finished medicinal product*.

The table shall contain information on all manufacturing sites comprising the manufacturing process of the finished medicinal product including manufacturing sites involved in the manufacturing of solvents and diluents and other participants of the manufacturing process of the finished medicinal product. The information on such manufacturing sites shall appear in the appropriate cells beneath each manufacturing step.

In each cell of the table, all participants of a particular process step shall appear. Where several manufacturing sites perform a particular manufacturing step, the appropriate number of rows corresponding to the number of manufacturing sites shall be added in the table template of the certificate.

20. Where specific conditions of the marketing authorization are envisaged, the Annex to the certificate shall contain a table *Specific conditions of the marketing authorization* (as a separate annex). In the left-hand column, the restrictions regarding medicinal product use shall be included; in the central column, additional obligations to be fulfilled as conditions of marketing authorization shall be included; in the right-hand column, the deadline for fulfilling obligations and restrictions imposed shall appear in DD.MM.YYYY format.

The Annex shall be integral part of the Certificate. Certificate shall be paginated and indicate serial number of the Certificate, the position, signature, name of the Head of the competent authority (authorized person) issuing the Certificate; each page shall be sealed by the competent authority.

21. The field 'Head of the competent authority, signature, SEAL' shall be completed manu propria; using facsimile is not allowed.

APPENDIX 18
to the Rules of authorization
and assessment of medicinal products
for human use

MEMBER STATE CONCERNED COMMENTS TEMPLATE

(template)

Comments of the Member State concerned

Type of procedure ☐ Mutual recognition

☐ Decentralized

1. Day	
2. Comments from	

Application number	
Date	
Brand name of the medicinal product	
Active substance(s)	
Strength(s)	
Pharmaceutical form	
Presentation	
Applicant (the applicant's representative)	

<u>*<Member State of the Union>*</u> is hereby agree with the overall conclusion of the reference Member State and is willing to grant a marketing authorization for <u>*<applied medicinal product>*</u>.

or:

<u>*<Member State of the Union>*</u> considers that use of the medicinal product concerned may be associated with a serious potential risk to public health (see below), and is not thereby willing to grant a marketing authorization.

2. Serious potential risk to public health

2.1. Summary of product characteristics, medication guide (patient leaflet) and labeling

Detailed objections together with their grounds and cross-references to the sections of the marketing authorization application dossier, normative documents, scientific guidelines, literature publications, or assessors' opinions attached to the form

2.2. Module 3. "Quality"

Detailed objections together with their grounds and cross-references to the sections of the marketing authorization application dossier, normative documents, scientific guidelines, literature publications, or assessors' opinions attached to the form

2.3. Module 4. "Nonclinical data"

Detailed objections together with their grounds and cross-references to the sections of the marketing authorization application dossier, normative documents, scientific guidelines, literature publications, or assessors' opinions attached to the form

2.4. Module 5. "Clinical data"

Detailed objections together with their grounds and cross-references to the sections of the marketing authorization application dossier, normative documents, scientific guidelines, literature publications, or assessors' opinions attached to the form

3. List of comments

3.1. Module 1. "Comments related to the application, summary of product characteristics, medication guide (patient leaflet), or labelling (including the medicinal product name)"[1]

Give a list of comments grouping them into two categories: major objections and other comments.

3.2. Module 3. "Quality"

Give a list of comments grouping them into two categories: major objections and other comments.

3.3. Module 4. "Nonclinical Studies"

Give a list of comments grouping them into two categories: major objections and other comments.

3.4. Module 5. "Clinical Studies"

Give a list of comments grouping them into two categories: major objections and other comments.

4. Notice to applicants

Attention! Any email response shall be sent to our corporate email ____@____; personal emails shall not be used. The maximum email message size is 2 MB. Hard copy shall also be send to the following address <address>[2].

Name of the contact person in the Member State

✉

☎

💻

Assessors' name (if applicable):

Quality (Module 3):	Clinical data (Module 5)
✉	Pharmacokinetics
☎	✉
💻	☎
	💻

Nonclinical studies (Module 4):	Safety and efficacy
✉	✉
☎	☎
💻	💻

[1] Please note that for generic and biosimilar applications, where reference product is marketed within the Union, product name related comments shall be sent as soon as possible.

[2] Will be provided in accordance with the requirements of each Member State of the Union.

APPENDIX 19
to the Rules of authorization
and assessment of medicinal products
for human use

RULES
of variations to the marketing authorizations application dossier for medicinal products for human use

I. GENERAL PROVISIONS

1.1. Subject matter and scope

1.1.1. This Appendix lays down provisions concerning the processing of variations to the terms of all marketing authorizations (hereinafter referred to as variations) for medicinal products for human use authorized in Eurasian Economic Union (hereinafter referred to as the Union) in accordance with the Rules of authorization and assessment of medicinal products for human use (hereinafter referred to as the Rules of authorization of medicinal products) or where those products are subject to bringing into compliance with the requirements of the legal acts which constitute the law of the Union.

1.1.2. This Appendix shall not apply to transfers of a marketing authorization from one marketing authorization holder (hereinafter holder) to another.

1.1.3. Section II of this Appendix shall apply only to variations to the terms of marketing authorizations granted in accordance with section V.II or VI of the Rules of authorization of medicinal products under the mutual recognition procedure or decentralized procedure, as well as variations to the terms of marketing authorizations of medicinal products granted by more than one Member States of the Union (hereinafter referred to as Member States) and which have undergone (or are undergoing) bringing into compliance under section XIII of the Rules of authorization of medicinal products.

1.1.4. Section III of this Appendix shall apply only to variations to the terms of marketing authorizations granted in one Member State (reference Member State) in accordance with section V.I of the Rules of authorization of medicinal products, as well as variations to the authorization terms of medicinal products granted by one Member State and which have undergone (or are undergoing) bringing into compliance under section XIII of the Rules of authorization of medicinal products.

1.1.5. Section IV of this Appendix shall apply only to variations to the terms of marketing authorizations referred to in paragraphs 1.1.3 and 1.1.4 of this Appendix.

1.1.6. Rules concerning the examination of variations to the terms of marketing authorizations for medicinal products for human use are provided in Appendix 20 to the Rules of authorization of medicinal products.

1.2. Definitions

For the purposes of this Appendix, the following definitions shall apply:

‘Member State concerned’ means a Member State whose competent authority has granted a marketing authorization for the medicinal product in question;

‘Major variation of type II’ means a variation which is not an extension and which may have a significant impact on the quality, safety or efficacy of the medicinal product concerned;

‘Extension of a marketing authorization’ or ‘extension’ means a variation which is listed in Annex I and fulfils the conditions laid down therein;

‘Variation to the terms of a marketing authorization’ or ‘variation’ means any amendment to:

Documents or particulars listed in Appendix 1 the Rules of authorization of medicinal products;

The terms of the decision granting the marketing authorization for a medicinal product for human use, including the summary of the product characteristics and any conditions, obligations, or restrictions affecting the marketing authorization, or changes to the labelling or the package leaflet connected with changes to the summary of the product characteristics;

'Minor variation of type IA' means a variation which has only a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned;

'**Minor variation of type IB'** means a variation which is neither a minor variation of type IA nor a major variation of type II nor an extension;

'**Urgent safety restriction**' means an interim change in the terms of the marketing authorization due to new information having a bearing on the safe use of the medicinal product;

'Relevant authority' means the competent authority (assessment organization) of each Member State concerned.

1.3. Classification of variations

1.3.1. In relation to any variation which is not an extension the classification laid down in Annex II shall apply.

1.3.2. A variation which is not an extension and whose classification is undetermined after application of the rules provided for in this Appendix, taking into account any recommendations delivered pursuant to paragraph 1.5, shall by default be considered a minor variation of type IB.

1.3.3. By way of derogation from 1.3.2, a variation which is not an extension and whose classification is undetermined after application of the rules provided for in this Appendix shall be considered a major variation of type II in the following cases:

upon request from the applicant when submitting the variation;

where the competent authority (assessment organization) of the reference Member State in consultation with the other competent authority (assessment organization) Member States concerned, or the competent authority in the case of a purely national marketing authorization, concludes, following the assessment of validity of a notification in accordance with paragraph 2.2.2 or 3.2.2 and taking into account the recommendations delivered pursuant to paragraph 1.5, that the variation may have a significant impact on the quality, safety or efficacy of the medicinal product concerned.

1.3.4. Details of the various categories of variations are provided in Annex V.

1.4. Variations

1.4.1. The Eurasian Economic Commission (hereinafter referred to as the Commission) shall regularly updated this Appendix taking into account scientific progress.

1.5. Recommendation on unforeseen variations

1.5.1. Prior to the submission of a variation whose classification is not provided for in this Appendix, a applicant may request from the competent authority (assessment organization) of the reference Member State a recommendation on the classification of the variation as follows:

1.5.2. The recommendation referred to in paragraph 1.5.1 shall be consistent with this Appendix. The competent authority (assessment organization) of the reference Member State within 45 calendar days following receipt of the request from the applicant shall delivered it and send it to the applicant, other Member States and the Expert Committee on medicinal products ate the Commission (hereinafter referred to as the Expert Committee) electronically and/or in paper format. The 45-day period referred to in the second subparagraph may be extended by 45 days where the relevant authority deems it necessary to consult with the Expert Committee.

1.5.3. Prior to the examination of a variation whose classification is not provided for in this Appendix, a competent authority (assessment organization) of a Member State may request a recommendation on the classification of the variation to the Expert Committee.

1.5.4. The recommendation referred to in paragraph 1.5.3 shall be consistent with this Appendix. It shall be delivered within 45 days following receipt of the request from the

competent authority (assessment organization) of a Member State concerned and sent to the applicant, the Expert Committee, and the appropriate competent authorities of Member States.

1.5.5. The Commission, based on paragraphs 1.5.1 and 1.5.3 to ensure the coherence of the recommendations delivered by the competent authorities (assessment organizations) of a Member States and the Expert Committee, shall publish those recommendations on its official web-site after deletion of all information of commercial confidential nature.

1.6. Variations leading to the revision of product information

1.6.1. Where a variation leads to the revision of the summary of product characteristics, labelling or package leaflet, this revision shall be considered as part of that variation.

1.7. Grouping of variations

1.7.1. Where several variations are notified or applied for, a separate notification or application for a variation to the terms of the marketing authorization for a medicinal product (hereinafter referred to as variation application) in accordance with Section II of this Appendix or paragraph 4.1.1 as appropriate shall be submitted in respect of each variation sought.

1.7.2. By way of derogation from paragraph 1.7.1, the following shall apply:

where the same minor variation(s) of type IA to the terms of one or more marketing authorizations owned by the same holder are notified at the same time to the same relevant authority, a single notification as referred to in paragraph 2.1 or 3.1 of this Appendix may cover all such variations;

where several variations to the terms of the same marketing authorization are submitted at the same time, a single submission may cover all such variations provided that the variations concerned fall within one of the cases listed in Annex III;

where several variations to the terms of the same marketing authorization are submitted at the same time and the variations do not fall within one of the cases listed in Annex III, a single submission may cover all such variations provided that the competent authority (assessment organization) of the reference Member State in consultation with the competent authorities (assessment organizations) of the Member States concerned agrees to such single submission.

1.7.3. The submission referred to in subparagraphs 1.7.2(2) and (3) of this Appendix shall be made simultaneously to all relevant authorities by means of the following:

a single notification in accordance with paragraph 2.2 where at least one of the variations is a minor variation of type IB and the remaining variations are minor variations;

a single application in accordance with paragraph 2.3 where at least one of the variations is a major variation of type II and none of the variations is an extension;

a single application in accordance with paragraph 4.1.1 where at least one of the variations is an extension.

II. VARIATIONS TO MARKETING AUTHORIZATIONS GRANTED IN MORE THAN ONE MEMBER STATES

2.1. Notification procedure for minor variations of type IA

2.1.1. Where a minor variation of type IA is made, the applicant shall submit simultaneously to all relevant authorities (assessment organizations) an application in paper and/or electronic format as laid down in Appendix 2 to the Rules of authorization and assessment of medicinal products and confirmation that the relevant fees have been paid as required by the reference Member State legislation.

The applicant shall submit to the competent authority (assessment organization) of the reference Member State variation application (notification) containing the elements listed in Annex IV. This application shall be submitted within 365 calendar days (12 months) following the implementation of the variation. However, the application shall be submitted before the

implementation of the variation in the case of variations entailing amendments to product information as provided in paragraph 1.6 of this Appendix.

2.1.2. However, the notification shall be submitted immediately after the implementation of the variation in the case of minor variations requiring immediate notification for the continuous supervision of the medicinal product concerned.

2.1.3. The competent authority (assessment organization) of the reference Member State within 5 business days beginning with the day the variation application is submitted, having checked of completeness and accuracy of the format of the documents submitted, shall ensure the access of relevant authorities of Member States concerned to the variation application (notification) via Integrated System.

Within 30 days following receipt of the notification, the measures provided for in paragraph 2.4 of this Appendix shall be taken by the relevant competent authorities.

In the case of variations entailing amendments to product information as provided in paragraph 1.6 of this Appendix, relevant competent authorities within 10 business days beginning with the day referred to in paragraph 2.1.3, shall make publicly available the information on variations made in the Common Register together with the approved summary of product characteristics, medication guide, mock-ups of the packaging, normative document in accordance with the Procedure for establishing and maintaining the Common Register and shall issue the updated summary of product characteristics, medication guide, mock-ups of the packaging, normative document, certificate of the marketing authorization to the applicant, where necessary.

The relevant competent authorities (assessment organizations) may extend the periods referred to in subparagraphs 1, 2 and 3 of this paragraph to 90 calendar days where the applicant has submitted multiple groupings of variations in accordance with paragraphs 1.7.2 and 1.7.3 of this Appendix.

2.2. Notification procedure for minor variations of type IB

2.2.1. The applicant shall submit simultaneously to all relevant authorities (assessment organizations) an application in paper and/or electronic format as laid down in Appendix 2 to the Rules of authorization and assessment of medicinal products and confirmation that the relevant fees have been paid as required by the reference Member State legislation.

This applicant shall submit to the competent authority (assessment organization) of the reference Member State variation application (notification) containing the elements listed in Annex IV.

2.2.2. The competent authority (assessment organization) of the reference Member State within 5 business days beginning with the day the variation application is submitted, having checked of completeness and accuracy of the format of the documents submitted, shall ensure the access of relevant authorities of Member States concerned to the variation application (notification) via Integrated System for external and mutual trade of the Union (hereinafter referred to as the Integrated System).

If the notification fulfils the requirement laid down in paragraph 2.2.1 of this Appendix, the competent authority (assessment organization) of the reference Member State shall, after consulting the relevant authorities of the Member States concerned where needed, acknowledge receipt of a valid notification within 30 calendar days.

2.2.3. If within 30 calendar days following the acknowledgement of receipt of a valid notification, the competent authority (assessment organization) of the reference Member State has not sent the applicant an unfavorable opinion and refuse to amend the terms of the marketing authorization electronically or in paper format, the notification shall be deemed accepted by all relevant authorities.

2.2.4. Where the notification is accepted by the competent authority (assessment organization) of the reference Member State, the measures provided for in paragraph 2.4 of this Appendix shall be taken by the competent authority (assessment organization) of the reference Member State.

In the case of variations entailing amendments to product information as provided in paragraph 1.6 of this Appendix, relevant competent authorities (assessment organizations) within 10 business days beginning with the day referred to in paragraph 2.2.3, shall make publicly available the information on variations made in the Common Register together with the approved summary of product characteristics, medication guide, mock-ups of the packaging, normative document in accordance with the Procedure for establishing and maintaining the Common Register and shall issue the updated summary of product characteristics, medication guide, mock-ups of the packaging, normative document, certificate of the marketing authorization to the applicant, where necessary.

The relevant competent authorities (assessment organizations) may extend the periods referred to in paragraphs 2.2.3 and 2.2.4 to 90 calendar days where the applicant has submitted multiple groupings of variations in accordance with paragraphs 1.7.2 and 1.7.3 of this Appendix.

2.2.5. Where the competent authority (assessment organization) of the reference Member State is of the opinion that the notification cannot be accepted, it shall inform the applicant and the other relevant authorities of the Member States concerned on that decision electronically or in paper format within period referred to in paragraph 2.2.3 of this Appendix, stating the grounds on which its unfavorable opinion is based.

2.2.6. In case of an unfavorable outcome, the applicant may reapply to the competent authority (assessment organization) of the reference Member State the notification within 30 days to take due account of the grounds referred to in paragraph 2.2.5 of this Appendix.

The competent authority (assessment organization) of the reference Member State within 5 business days beginning with the day the amended variation application is submitted, having checked of completeness and accuracy of the format of the documents submitted, shall ensure the access of relevant authorities of Member States concerned to the variation application (notification) via Integrated System

2.2.7. If the applicant does not amend the notification in accordance with paragraph 2.2.6 of this Appendix, the notification shall be deemed rejected by all competent authorities (assessment organizations) and the measures provided for in Article 11 shall be taken.

2.2.8. Where an amended notification has been submitted, the competent authority of the reference Member State shall assess it within 30 days following its receipt and the measures provided for in paragraph 2.4 of this Appendix shall be taken.

In the case of variations entailing amendments to product information as provided in paragraph 1.6 of this Appendix, relevant competent authorities (assessment organizations) within 10 business days beginning with the day referred to in paragraph 2.2.8, shall make publicly available the information on variations made in the Common Register together with the approved summary of product characteristics, medication guide, mock-ups of the packaging, normative document in accordance with the Procedure for establishing and maintaining the Common Register and shall issue the updated summary of product characteristics, medication guide, mock-ups of the packaging, normative document, certificate of the marketing authorization to the applicant, where necessary.

The relevant competent authorities (assessment organizations) may extend the periods referred to in subparagraphs 1 and 2 of this paragraph to 90 calendar days where the applicant has submitted multiple groupings of variations in accordance with paragraphs 1.7.2 and 1.7.3 of this Appendix.

2.2.9. Paragraphs 2.2.1 to 2.2.8 of this Appendix shall not apply where a type IB variation request is submitted in a grouping that includes a variation type II and does not contain an extension. In such case, the assessment procedure in paragraph 2.3 of this Appendix shall apply.

2.2.10. Paragraphs 2.2.1 to 2.2.8 of this Appendix shall not apply where a type IB variation request is submitted in a grouping that includes an extension. In such case, the procedure in paragraph 4.1.1 of this Appendix shall apply.

2.3. Assessment procedure for major variations of type II

2.3.1. The applicant shall submit simultaneously to all relevant authorities (assessment organizations) an application in paper and/or electronic format as laid down in Appendix 2 to the Rules of authorization and assessment of medicinal products and confirmation that the relevant fees have been paid as required by the reference Member State legislation.

This applicant shall submit to the competent authority (assessment organization) of the reference Member State variation application (notification) containing the elements listed in Annex IV.

Where needed and subject to agreement with the assessment organization, applicant shall submit samples of finished products, the reference standards of active substances and product-related impurities, specific reagents, and other materials necessary to carry out the laboratory testing to the competent authority (assessment organization) of the reference Member State.

2.3.2. The applicant shall submit missing particulars upon observations of the competent authority (assessment organization) of the reference Member State within a maximum of 90 calendar days which is excluded from the period designated for assessment and processing the variation.

The competent authority (assessment organization) of the reference Member State shall refuse the variation application to the terms of marketing authorization for a medicinal product in case of failure to submit the particulars in response to the observations of the competent authority (assessment organization) of the reference Member State and/or failure to pay fees for variation to the terms of marketing authorization, as required by the reference Member State legislation.

The competent authority (assessment organization) of the reference Member State within 14 business days beginning with the day the variation application is submitted, having checked of completeness and accuracy of the format of the documents submitted, shall ensure the access of relevant authorities of Member States concerned to the variation application (notification) via Integrated System.

Written communications between competent authorities (assessment organizations) of the reference Member State and Member States concerned shall be implemented electronically via the Integrated System.

2.3.3. Within 60 calendar days following the acknowledgement of receipt of a valid application, the competent authority (assessment organization) of the reference Member State shall prepare an assessment report and a draft decision on the variation application, which shall be communicated to the other relevant authorities of the Member States concerned electronically and/or in paper format.

2.3.4. The competent authority (assessment organization) of the reference Member State may reduce the period referred to in paragraph 2.3.3 of this Appendix, having regard to the urgency of the matter, or extend it to 90 calendar days for variations concerning a change to or addition of therapeutic indications or for grouping of variations in accordance with paragraph 1.7.2(c) of this Appendix.

2.3.5. Within the period referred to in paragraphs 2.3.3 and 2.3.4, the competent authority (assessment organization) of the reference Member State may request the applicant in writing and/or electronically to provide supplementary information necessary to explain or clarify the documents or particulars provided in the marketing authorization application dossier (including proposals on amendments to the summary of product characteristics, medication guide, mock-ups of the packaging of the medicinal product, normative document or other documents of the marketing authorization application dossier).

The competent authority (assessment organization) of the reference Member State shall send copies of the requests to the applicant to the relevant authorities of the Member States concerned using the templates provided in Appendices 6 to 8 to the Rules of authorization and assessment of medicinal products.

The period to response by the applicant to that request should be a maximum of 90 calendar days.

The period for providing these documents requested by the competent authority or assessment organization by the applicant is not to be counted in the period of the assessment and processing of the variation.

If the applicant does not provide the requested documents or particulars in due time, the assessment and processing of the variation shall be terminated. The competent authority (assessment organization) of the reference Member State shall inform the applicant and relevant authorities of the Member States concerned in writing or electronically on that decision within 10 calendar days beginning with the day such a decision is made.

2.3.6. Without prejudice to paragraph 2.6 of this Appendix and within 30 calendar days following receipt of the draft assessment report and of the draft decision referred to in paragraphs 2.3.3 and 2.3.4 of this Appendix, the competent authorities of the Member States shall recognize the assessment report drawn up by the assessment organization of the reference Member State and inform the competent authority (assessment organization) of the reference Member State accordingly.

The competent authority (assessment organization) of the Member State concerned may send a request to the applicant and competent authority (assessment organization) of the reference Member State using the template provided in Appendix 18 to the Rules of authorization and assessment of medicinal products within a maximum of 20 calendar days beginning with the day the access to the assessment report has been granted.

The period to response by the applicant to that request of the competent authority (assessment organization) of the Member State concerned and the reference Member State shall be a maximum of 90 calendar days. The period for providing requested documents by the applicant is not to be counted in the period of the assessment and processing of the variation.

If the applicant does not provide the documents or particulars requested by the competent authority (assessment organization) of the Member State concerned in due time, the assessment and the processing of the variation shall be terminated in that Member State concerned.

The applicant shall be informed in writing or electronically on that decision of the competent authority and/or assessment organization within 10 business days beginning with the day such a decision is made.

2.3.7. Where within the period referred to in paragraph 2.3.6(1) the competent authority (assessment organization) of the Member State concerned does not send its opinion not recognizing the assessment report drawn up by the assessment organization of the reference Member State, the decision is deemed to made by that competent authority (assessment organization).

2.3.8. Where the decision referred to in paragraph 2.3.7 of this Appendix has been recognized by all competent authorities in accordance to paragraphs 2.3.6 and 2.3.7 of this Appendix, the measures provided for in paragraph 2.4 of this Appendix shall be taken.

In the case of variations entailing amendments to product information as provided in paragraph 1.6 of this Appendix, relevant competent authorities (assessment organizations) within 10 business days beginning with the day the favorable decision is made, shall make publicly available the information on variations made in the Common Register together with the approved summary of product characteristics, medication guide, mock-ups of the packaging, normative document in accordance with the Procedure for establishing and maintaining the Common Register and shall issue the updated summary of product characteristics, medication guide, mock-ups of the packaging, normative document, certificate of the marketing authorization to the applicant, where necessary.

The competent authorities may extend the periods referred to in subparagraph 1 of this paragraph to 30 calendar days where the applicant has submitted multiple groupings of variations in accordance with paragraphs 1.7.2 and 1.7.3 of this Appendix.

2.3.9. This section shall not apply where a type II variation request is submitted in a grouping that includes an extension. In such case, the procedure in paragraph 4.1.1 of this Appendix shall apply.

2.4. Measures to close the procedures of paragraphs 2.3 to 2.5 of this Appendix

2.4.1. Where reference is made to this paragraph, the competent authority (assessment organization) of the reference Member State shall take the following measures:

it shall inform the applicant and the relevant authorities of the Member States concerned as to whether the variation is accepted or rejected;

where the variation is rejected, it shall inform the applicant and the relevant authorities of the Member States concerned of the grounds for the rejection;

it shall inform the applicant and the relevant authorities of the Member States concerned as to whether the variation requires any amendment to the decision granting the marketing authorization including the summary of product characteristics and any conditions, obligations, or restrictions which may impact on the marketing authorization decision or amendment to the labelling or patient leaflet due to amendment to the summary of product characteristics due to amendment the latter.

2.4.2. Where reference is made to this paragraph, each competent authority shall, where necessary and within the time limit laid down in paragraph 4.2.1 of this Appendix (except for amendments to product information as provided in paragraph 1.6 of this Appendix), amend the decision granting the marketing authorization in accordance with the accepted variation.

2.5. Expert Committee procedure

2.5.1. Where the competent authority of one or more Member States concerned sends an opinion not recognizing the assessment report drawn up by the assessment organization of the reference Member State, in accordance to paragraphs 4.1.2.9, 2.3.6, and 2.3.7 of this Appendix, the Expert Committee shall carry out a procedure to consider the disagreement as laid down in the Rules of Procedure subject to approval by the Commission, within a maximum of 60 calendar days beginning with the day the competent authorities of the Member States concerned sent that opinion.

2.5.2. The competent authority of the reference Member State and of relevant Member States concerned shall refuse to amend the terms of the marketing authorization if based on the outcome of the assessment of the medicinal product and upon completion of the procedure of resolving disagreement in the Expert Committee the recommendation is made to refuse to amend the terms of the marketing authorization.

III. VARIATIONS TO PURELY NATIONAL MARKETING AUTHORIZATIONS (IN A REFERENCE MEMBER STATE ONLY)

3.1. Notification procedure for minor variations of type IA

3.1.1. Where a minor variation of type IA is made, the applicant shall submit to the competent authority (assessment organization) an application in paper and/or electronic format as laid down in Appendix 2 to the Rules of authorization and assessment of medicinal products, confirmation that the relevant fees have been paid as required by the Member States legislation and an application containing the elements listed in Annex IV. This application shall be submitted within 365 calendar days (12 months) following the implementation of the variation. However, the application shall be submitted before the implementation of the variation in the case of variations entailing amendments to product information as provided in paragraph 1.6 of this Appendix.

3.1.2. However, the notification shall be submitted immediately after the implementation of the variation in the case of minor variations requiring immediate notification for the continuous supervision of the medicinal product concerned.

3.1.3. Within 30 days following receipt of the notification, the measures provided for in paragraph 3.5 of this Appendix shall be taken by the competent authority (assessment organization) of the reference Member State.

In the case of variations entailing amendments to product information as provided in paragraph 1.6 of this Appendix, competent authority of the reference Member State within 10 business days beginning with the day referred to in paragraph 3.1.3, shall make publicly available the information on variations made in the Common Register together with the approved summary of product characteristics, medication guide, mock-ups of the packaging, normative document in accordance with the Procedure for establishing and maintaining the Common Register and shall issue the updated summary of product characteristics, medication guide, mock-ups of the packaging, normative document, certificate of the marketing authorization to the applicant, where necessary.

The competent authority (assessment organization) of the reference Member State may extend the periods referred to in subparagraphs 1 or 2 of this paragraph to 90 calendar days where the applicant has submitted multiple groupings of variations in accordance with paragraphs 1.7.2 and 1.7.3 of this Appendix.

3.2. Notification procedure for minor variations of type IB

3.2.1. The applicant shall submit to the competent authority (assessment organization) an application in paper and/or electronic format as laid down in Appendix 2 to the Rules of authorization and assessment of medicinal products, confirmation that the relevant fees have been paid as required by the Member State legislation, and an application containing the elements listed in Annex IV.

3.2.2. The competent authority (assessment organization) of the reference Member State within 5 business days beginning with the day the variation application is submitted shall check completeness and accuracy of the format of the documents submitted under paragraph 3.2.1 of this Appendix.

If the notification fulfils the requirement laid down in paragraph 3.2.1 of this Appendix, the competent authority (assessment organization) of the reference Member State shall acknowledge receipt of a valid notification within 30 calendar days.

3.2.3. If within 30 calendar days following the acknowledgement of receipt of a valid notification, the competent authority (assessment organization) has not sent the applicant an unfavorable opinion and refusal to amend the terms of the marketing authorization electronically or in paper format, the notification shall be deemed accepted by the competent authority.

3.2.4. Where the notification is accepted by the competent authority (assessment organization) of the reference Member State, the measures provided for in paragraph 3.4 of this Appendix shall be taken by the competent authority (assessment organization) of the reference Member State.

In the case of variations entailing amendments to product information as provided in paragraph 1.6 of this Appendix, relevant competent authority (assessment organization) of the reference Member State within 10 business days beginning with the day referred to in paragraph 3.2.3, shall make publicly available the information on variations made in the Common Register together with the approved summary of product characteristics, medication guide, mock-ups of the packaging, normative document in accordance with the Procedure for establishing and maintaining the Common Register and shall issue the updated summary of product characteristics, medication guide, mock-ups of the packaging, normative document, certificate of the marketing authorization to the applicant, where necessary.

The competent authority (assessment organization) of the reference Member State may extend the periods referred to in paragraphs 3.2.3 and 3.2.4 of this Appendix to 90 calendar days where the applicant has submitted multiple groupings of variations in accordance with paragraphs 1.7.2 and 1.7.3 of this Appendix.

3.2.5. Where the competent authority (assessment organization) of the reference Member State is of the opinion that the notification cannot be accepted, it shall inform the applicant on that decision electronically or in paper format within period referred to in paragraph 3.2.3 of this Appendix, stating the grounds on which its unfavorable opinion is based.

3.2.6. In case of an unfavorable outcome, the applicant may reapply to the competent authority (assessment organization) of the reference Member State the notification within 30 days to take due account of the grounds referred to in paragraph 3.2.5 of this Appendix.

3.2.7. If the applicant does not amend the notification in accordance with paragraph 3.2.6 of this Appendix, the notification shall be deemed rejected.

3.2.8. Where an amended notification has been submitted, the competent authority (assessment organization) of the reference Member State shall assess it within 30 days following its receipt and the measures provided for in paragraph 3.5 of this Appendix shall be taken.

3.2.9. This Section shall not apply where a type IB variation request is submitted in a grouping that includes a variation type II and does not contain an extension. In such case, the assessment procedure in paragraph 3.3 of this Appendix shall apply.

3.2.10. This Section shall not apply where a type IB variation request is submitted in a grouping that includes an extension. In such case, the procedure in paragraph 4.1.1 of this Appendix shall apply.

3.3. Assessment procedure for major variations of type II

3.3.1. The applicant shall submit to the competent authority (assessment organization) an application in paper and/or electronic format as laid down in Appendix 2 to the Rules of authorization and assessment of medicinal products, confirmation that the relevant fees have been paid as required by the Member States legislation and an application containing the elements listed in Annex IV.

Where needed and subject to agreement with the assessment organization, applicant shall submit samples of finished products, the reference standards of active substances and product-related impurities, specific reagents, and other materials necessary to carry out the laboratory testing to the competent authority (assessment organization) of the reference Member State.

3.3.2. The competent authority (assessment organization) of the reference Member State within 14 business days beginning with the day the variation application is submitted to the reference Member State shall check completeness and accuracy of the format of the documents submitted under paragraph 3.3.1 of this Appendix.

If the application fulfils the requirements laid down in paragraph 3.3.1 of this Appendix, the competent authority (assessment organization) shall acknowledge receipt of a valid application.

The applicant shall submit missing particulars upon observations of the competent authority (assessment organization) of the reference Member State within a maximum of 90 calendar days which is excluded from the period designated for assessment and processing the variation.

The competent authority (assessment organization) of the reference Member State shall refuse the variation application to the terms of marketing authorization for a medicinal product in case of failure to submit the particulars in response to the observations of the competent authority (assessment organization) of the reference Member State and/or failure to pay fees for variation to the terms of marketing authorization, as required by the reference Member State legislation.

3.3.3. Within 60 calendar days following the acknowledgement of receipt of a valid application referred to in paragraph 3.3.1 of this Appendix, the competent authority (assessment organization) of the reference Member State shall finalize the assessment of the medicinal product and prepare an assessment report.

3.3.4. The competent authority (assessment organization) may reduce the period referred to in paragraph 3.3.3 of this Appendix, having regard to the urgency of the matter, or extend it to 90 calendar days for variations concerning a change to or addition of therapeutic indications or for grouping of variations in accordance with paragraph 3.4.2(3) of this Appendix.

3.3.5. The period referred to in paragraph 3.3.3 of this Appendix shall be 90 days for variations listed in paragraph 2 of Annex I.

3.3.6. Within the period referred to in paragraphs 3.3.3 to 3.3.5 of this Appendix, the competent authority (assessment organization) may request the applicant in writing and/or electronically to provide supplementary information necessary to explain or clarify the documents or particulars provided in the marketing authorization application dossier (including proposals on amendments to the summary of product characteristics, medication guide, mock-ups of the packaging of the medicinal product, normative document or other documents of the marketing authorization application dossier).

The period to response by the applicant to that request should be a maximum of 90 calendar days.

The period for providing these documents requested by the competent authority or assessment organization by the applicant is not to be counted in the period of the assessment and processing of the variation.

If the applicant does not provide the requested documents or particulars in due time, the assessment and processing of the variation shall be terminated. The competent authority (assessment organization) of the reference Member State shall inform the applicant in writing or electronically on that decision within 10 calendar days beginning with the day such a decision is made.

3.3.7. Within 10 business day beginning with the day the assessment has been finalized, the measures provided for in paragraph 3.5 of this Appendix shall be taken.

In the case of variations entailing amendments to product information as provided in paragraph 1.6 of this Appendix, relevant competent authority of the reference Member State within 10 business days beginning with the day the assessment has been finalized, shall make publicly available the information on variations made in the Common Register together with the approved summary of product characteristics, medication guide, mock-ups of the packaging, normative document in accordance with the Procedure for establishing and maintaining the Common Register and shall issue the updated summary of product characteristics, medication guide, mock-ups of the packaging, normative document, certificate of the marketing authorization to the applicant, where necessary.

The competent authority may extend the periods referred to in subparagraph 1 of this paragraph to 30 calendar days where the applicant has submitted multiple groupings of variations in accordance with paragraphs 1.7.2 and 1.7.3 of this Appendix.

3.3.8. This section shall not apply where a type II variation request is submitted in a grouping that includes an extension. In such case, the procedure in paragraph 4.1.1 of this Appendix shall apply.

3.4. Grouping of variations to purely national marketing authorizations (in a reference Member State only)

3.4.1. Where several variations are notified or applied for, a separate notification or application in accordance with paragraph 3.1, 3.2, or 3.3 of this Appendix, or paragraph 4.1.1 as appropriate shall be submitted to the competent authority in respect of each variation sought.

3.4.2. By way of derogation from paragraph 3.4.1 of this Appendix the following shall apply:

where the same minor variation(s) of type IA to the terms of one or more marketing authorizations owned by the same holder are notified at the same time to the same relevant authority, a single notification as referred to in paragraph 3.1 of this Appendix may cover all such variations;

where several variations to the terms of the same marketing authorization are submitted at the same time to the same competent authority (assessment organization), a single submission may cover all such variations provided that the variations concerned fall within one of the cases listed in Annex III;

where several variations to the terms of the same marketing authorization are submitted at the same time to the same competent authority (assessment organization) and the variations do not fall within one of the cases listed in Annex III, a single submission may cover all such

variations provided that the competent authority (assessment organization) of the reference Member State agrees to such single submission.

3.4.3. The submission referred to in subparagraphs 3.4.2(2) and (3) of this Appendix shall be made simultaneously by means of the following:

a single notification in accordance with paragraph 3.2 of this Appendix where at least one of the variations is a minor variation of type IB and the remaining variations are minor variations;

a single application in accordance with paragraph 3.3 of this Appendix where at least one of the variations is a major variation of type II and none of the variations is an extension;

a single application in accordance with paragraph 4.1.1 of this Appendix where at least one of the variations is an extension.

3.5. Measures to close the procedures of Articles 3.1 to 3.3 of this Appendix

3.5.1. Where reference is made to this paragraph, the competent authority (assessment organization) of the reference Member State shall take the following measures:

it shall inform the applicant as to whether the variation is accepted or rejected;

where the variation is rejected, it shall inform the applicant of the grounds for the rejection;

where necessary and within the time limit laid down in paragraph 4.2.1 of this Appendix, competent authority of the reference Member State shall amend the decision granting the marketing authorization referred to in paragraph 1.2.1(b) in accordance with the accepted variation.

IV. OTHER ASPECTS

4.1. Special procedures

4.1.1. Extensions of marketing authorizations

An application for an extension of a marketing authorization shall be evaluated in accordance with the same procedure as for the initial marketing authorization to which it relates as laid down in sections V and VI of Rules of authorization of medicinal products.

An extension shall either be granted a marketing authorization in accordance with the same procedure as for the granting of the initial marketing authorization to which it relates or be included in that marketing authorization.

4.1.2. Work-sharing procedure

By way of derogation from paragraphs 1.7.1, 2.3 and 2.4 of this Appendix, where a minor variation of type IB, a major variation of type II, or a group of variations as provided for in paragraphs 1.7.2 of this Appendix that does not contain any extension relates to several marketing authorizations owned by the same holder, the holder of such marketing authorizations may follow the procedure provided in this paragraph.

For the purposes of this paragraph, ‘reference authority’ shall mean the competent authority of a Member State concerned chosen by the Expert Committee, taking into account a recommendation of the holder.

The applicant shall submit to all relevant authorities an application containing the elements listed in Annex IV, with an indication of the preferred reference authority.

If the application fulfils the established requirements, the Expert Committee shall choose a reference authority, and that reference authority shall acknowledge receipt of a valid application.

Where the chosen reference authority is the competent authority of a reference Member State which has not granted a marketing authorization for all the medicinal products affected by the application, the Expert Committee may request another relevant authority to assist the reference authority in the evaluation of that application.

The reference authority shall issue an opinion on a valid application within a period of 60 calendar days following acknowledgement of receipt of a valid application in the case of minor variations of type IB or major variations of type II.

The reference authority may reduce the that period, having regard to the urgency of the matter, or extend it to 90 calendar days for variations concerning a change to or addition of therapeutic indications.

Within the that period, the reference authority may request the applicant to provide supplementary information within a time limit set by the reference authority. In this case:

the reference authority shall inform the other relevant authorities of its request for supplementary information;

the procedure shall be suspended until such supplementary information has been provided;

the reference authority may extend the that period.

The reference authority shall send its opinion on the valid application to the applicant and other competent authorities, and within 30 calendar days beginning with the receipt of that opinion relevant authorities shall approve that opinion, inform the reference authority and update the terms of marketing authorizations concerned accordingly.

In view of verification of validity of the variation application and making an opinion on valid variation application, upon request of the reference authority, the Member States concerned shall provide information on variations to the terms of marketing authorizations concerned.

4.1.3. Pandemic situation with respect to human influenza

By way of derogation from Section I, II, and III, where a pandemic situation with respect to human influenza is duly recognized by the World Health Organisation or by the Union, the competent authorities may exceptionally and temporarily accept a variation to the terms of a marketing authorization for a human influenza vaccine, where certain non-clinical or clinical data are missing.

Where a variation is accepted pursuant to paragraph 1, the applicant shall submit the missing non-clinical and clinical data within a time limit set by the relevant authority.

4.1.4. Urgent safety restrictions

Where, in the event of a risk to public health in the case of medicinal products for human use the holder takes urgent safety restrictions on its own initiative, it shall forthwith inform all relevant authorities of the Member States.

If the relevant authority has not raised objections within 24 hours following receipt of that information, the urgent safety restrictions shall be deemed accepted.

In the event of a risk to public health in the case of medicinal products for human use relevant authorities may impose urgent safety restrictions on the holder.

Where an urgent safety restriction is taken by the holder or imposed by a relevant authority, the holder shall submit the corresponding application for variation within 15 days following the initiation of that restriction to the competent authority (assessment organization).

4.2. Amendments to the decision granting the marketing authorization and implementation

4.2.1. Amendments to the decision granting the marketing authorization

Amendments to the decision granting the marketing authorization resulting from the procedures laid down in Chapters II and III of this Appendix shall be made:

in the case of major variations of type II, within 60 calendar days following receipt of the information referred to in paragraph 2.4.1(4) or 3.5.1(2) of this Appendix, provided that all the documents necessary for the amendment of the marketing authorization have been transmitted to the competent authorities (assessment organizations) of the Member States concerned;

in the other cases, within 180 calendar days following receipt of the information referred to paragraph 2.4.1(4) or 3.5.1(2) of this Appendix, provided all the documents necessary for the amendment of the marketing authorization have been transmitted to the competent authorities (assessment organizations) of the Member States concerned.

Where the decision granting a marketing authorization is amended as a result of one of the procedures laid down in Chapters II, III, and IV of this Appendix, the relevant authority shall notify the amended decision without delay to the applicant.

4.2.2. Implementation of variations

Minor variations of type IA may be implemented any time before completion of the procedures laid down in paragraph 2.1 or 3.1 of this Appendix.

Where a notification concerning one or several minor variations of type IA is rejected, the applicant shall cease to apply the concerned variation(s) immediately after receipt of the information referred to in paragraph 2.4.1(4) or 3.5.1(2) of this Appendix.

Minor variations of type IB may only be implemented in the following cases:

for variations submitted in accordance with the procedures laid down in Chapter II, after the competent authority (assessment organization) of the reference Member State has informed the applicant that it has accepted the notification pursuant to paragraph 2.2, or after the notification is deemed accepted pursuant to paragraph 2.2.3;

for variations submitted in accordance with the procedures laid down in section III, after the relevant authority has informed the applicant that competent authority (assessment organization) has accepted the notification pursuant to paragraph 3.2, or after the notification is deemed accepted pursuant to paragraph 3.2.3;

for variations submitted in accordance with the procedure laid down in paragraph 4.2.1, after the reference authority has informed the applicant that its opinion is favorable.

Any variations entailing amendments to product information as provided in paragraph 1.6 of this Appendix may be implemented after the variations have been processed.

Major variations of type II may only be implemented in the following cases:

for variations submitted in accordance with the procedures laid down in Section II, 30 calendar days after the competent authority (assessment organization) of the reference Member State has informed the applicant that it has accepted the variation pursuant to paragraph 2.3, under the condition that the documents necessary for the amendment to the marketing authorization have been provided to the relevant authorities of the Member States concerned. Where an arbitration procedure has been initiated in accordance with paragraph 2.6, the applicant shall not implement the variation until the arbitration procedure has concluded that the variation is accepted;

for variations submitted in accordance with the procedures laid down in Section III, after the competent authority has informed the applicant that it has accepted the variation pursuant to paragraph 3.3;

for variations submitted in accordance with the procedures laid down in paragraph 4.1.2, 30 calendar days after the reference authority has informed the applicant that its opinion is favorable, under the condition that the documents necessary for the amendment to the marketing authorization have been provided to the Member States concerned; unless an arbitration procedure has been initiated in accordance with paragraph 2.6. Where an arbitration procedure has been initiated in accordance with paragraph 2.6, the applicant shall not implement the variation until the arbitration procedure has concluded that the variation is accepted.

Any variations entailing amendments to product information as provided in paragraph 1.6 of this Appendix may be implemented after the variations have been processed.

An extension may only be implemented after the relevant authority has amended the decision granting the marketing authorization and notified the applicant accordingly.

Urgent safety restrictions and variations which are related to safety issues shall be implemented within a time frame agreed by the applicant and the relevant authority.

By way of derogation from the first subparagraph, urgent safety restrictions and variations related to safety issues which concern marketing authorizations shall be implemented within a time frame agreed by the holder (applicant) and the competent authority of the reference Member State, in consultation with the other relevant authorities.

V. FINAL PROVISIONS

5.1. Continuous monitoring

Where requested by a relevant authority, the applicant shall supply without delay any information related to the implementation of a given variation.

5.2. Review of this document

By five years from the date the Rules of authorization and assessment of medicinal products for human use become effective, the Expert Committee shall assess the application of

this document as regards the classification of variations, with a view to proposing any necessary amendments to adapt Annexes I and II to take account of scientific and technical progress.

ANNEX I
Extensions of marketing authorizations

1. Changes to the active substance(s):

a) replacement of a chemical active substance by a different salt/ester complex/derivative, with the same therapeutic moiety, where the efficacy/safety characteristics are not significantly different;

b) replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer), where the efficacy/safety characteristics are not significantly different;

c) replacement of a biological active substance with one of a slightly different molecular structure where the efficacy/safety characteristics are not significantly different, with the exception of changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

d) modification of the vector used to produce the antigen or the source material, including a new master cell bank from a different source, where the efficacy/safety characteristics are not significantly different;

e) a new ligand or coupling mechanism for a radiopharmaceutical, where the efficacy/safety characteristics are not significantly different;

f) change to the extraction solvent or the ratio of herbal drug to herbal drug preparation where the efficacy/safety characteristics are not significantly different.

2. Changes to strength, pharmaceutical form and route of administration:

a) change of bioavailability;

b) change of pharmacokinetics e.g. change in rate of release;

c) change or addition of a new strength/potency;

d) change or addition of a new pharmaceutical form;

(e) change or addition of a new route of administration (for parenteral administration, it is necessary to distinguish between intra-arterial, intravenous, intramuscular, subcutaneous and other routes).

ANNEX II
Classification of variations

1. The following variations shall be classified as minor variations of type IA:

a) variations of purely administrative nature that are related to the identity and contact details of:

the holder, applicant, holder’s representative;

the manufacturer or supplier of any starting material, reagent, intermediate, active substance used in the manufacturing process or finished product;

b) variations related to the deletion of any manufacturing site, including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place;

c) variations related to minor changes to an approved physicochemical test procedure, where the updated procedure is demonstrated to be at least equivalent to the former test procedure, appropriate validation studies have been performed and the results show that the updated test procedure is at least equivalent to the former (to be replaced);

d) variations related to changes made to the specifications of the active substance or of an excipient in order to comply with an update of the relevant monograph of the Pharmacopoeia of the Union or of the pharmacopoeia of a Member State, where the change is made exclusively to comply with the pharmacopoeia and the specifications (normative document) for product specific properties are unchanged;

e) variations related to changes in the packaging material not in contact with the finished product, which do not affect the delivery, use, safety or stability of the medicinal product;

f) variations related to the tightening of specification limits, where the change is not a consequence of any commitment from previous assessment to review specification (normative document) limits and does not result from unexpected events arising during manufacture.

2. The following variations shall be classified as major variations of type II:

a) variations related to the addition of a new therapeutic indication or to the modification of an existing one;

b) variations related to significant modifications of the summary of product characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance findings;

c) variations related to changes outside the range of approved specifications, limits or acceptance criteria;

d) variations related to substantial changes to the manufacturing process, formulation, specifications (normative document) or impurity profile of the active substance or finished medicinal product which may have a significant impact on the quality, safety or efficacy of the medicinal product;

e) variations related to modifications in the manufacturing process or sites of the active substance for a biological medicinal product;

f) variations related to the introduction of a new design space or the extension of an approved one, where the design space has been developed in accordance with the relevant Union and international scientific guidelines;

j) variations related to changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

ANNEX III

Cases for grouping variations referred to in paragraph 1.7.2(3) and paragraph 3.4.2(3)

1. One of the variations in the group is an extension of the marketing authorization.

2. One of the variations in the group is a major variation of type II; all other variations in the group are variations which are consequential to this major variation of type II.

3. One of the variations in the group is a minor variation of type IB; all other variations in the group are minor variations which are consequential to this minor variation of type IB.

4. All variations in the group relate solely to changes of administrative nature to the summary of product characteristics, labelling and package leaflet or insert.

5. All variations in the group are changes to an Active Substance Master File, Vaccine Antigen Master File or Plasma Master File.

6. All variations in the group relate to a project intended to improve the manufacturing process and the quality of the medicinal product concerned or its active substance(s).

7. All variations in the group are changes affecting the quality of a human pandemic influenza vaccine.

8. All variations in the group are changes to the pharmacovigilance system.

9. All variations in the group are consequential to a given urgent safety restriction and submitted in accordance with paragraph 4.1.4 of this document.

10. All variations in the group relate to the implementation of a given class labelling in the summary of product characteristics, labelling, or patient leaflet (e.g. introduction of a class warning).

11. All variations in the group are consequential to the assessment of a given periodic safety update report.

12. All variations in the group are consequential to a given post-authorization study conducted under the supervision of the holder.

13. All variations in the group are consequential to a specific obligation imposed by the competent authority of a Member Stated within granting the marketing authorization.

14. All variations in the group are consequential to a conditional marketing authorization.

ANNEX IV
Documents to be submitted by the applicant to amend the terms of terms of marketing authorizations for medicinal products (variation application)

1. A list of all the marketing authorizations application dossiers affected by the notification or application.

2. A description of all the variations submitted, including:

in the case of minor variations of type IA, the date of implementation for each variation described;

in the case of minor variations of type IA which do not require immediate notification, a description of all minor variations of type IA made in the last 365 calendar days (12 months) to the terms of the concerned marketing authorization(s) and which have not been already notified.

3. All necessary documents as listed in Annex V to this document in relation to the appropriate variation. Where those documents are submitted in any language other than Russian, the authentic translation into Russian shall be supplemented.

4. Where a variation leads to or is the consequence of other variations to the terms of the same marketing authorization, a description of the relation between these variations.

5. Confirmation that the fees for variations to the terms of the marketing authorization for a medicinal product have been paid as required by the reference Member State legislation.

6. A list of Member States concerned with an indication of the reference Member State if applicable.

ANNEX V.
Classification of variations to the marketing authorization application dossier for a medicinal product

Variations to the terms of the marketing authorization for medicinal products shall be classified in accordance with this Annex as follows:

Administrative changes;

Quality changes;

Safety, Efficacy and Pharmacovigilance changes

Specific changes to Plasma Master Files and Vaccine Antigen Master Files.

Where reference has to be made to specific variations in this Annex, the variation in question should be quoted using the following structure:

X.N.x.n (‘variation code’),

where:

X refers to the capital letter of the chapter in this Annex where the variation is included (e.g. A, B, C or D)

N refers to the roman number of the section inside a chapter where the variation is included (e.g. I, II, III, etc.)

x refers to the letter of the subsection inside a chapter where the variation is included (e.g. a, b, c, etc.)

n refers to the number given in this Annex to a specific variation (e.g. 1, 2, 3, etc.)

For each chapter this Annex contains:

A list of variations which should be classified as minor variations of Type IA or major variations of Type II in accordance with the definitions of paragraph 1.2 of this document and Annex II of this document. It is also indicated which minor variations of Type IA require immediate notification as established in paragraphs 2.1.2 and 3.1.2 of this Appendix;

A list of variations which should be classified as minor variations of Type IB. In accordance with the definitions of paragraph 1.3 of this document, this category shall be assigned by default. In this regard, this Annex is not intended to establish the exhaustive list of such type of variations;

The Annex V does not deal with the classification of extensions as they are exhaustively listed in Annex I of this document. All changes specified in Annex I of this document must be considered extensions of the marketing authorizations. Any other change cannot be classified as such.

When one or more of the conditions established in this Annex for a minor variation of Type IA are not met, the concerned change may be submitted as a Type IB variation ('Type IB by default') unless the change is specifically classified as a major variation of Type II in this Annex or in a recommendation pursuant to paragraph 1.5 of this document, or unless the applicant considers that the changes may have a significant impact on the quality, safety or efficacy of the medicinal product.

If the competent authority considers that a variation submitted as a Type IB by default may have a significant impact on the quality, safety or efficacy of the medicinal product, it may request that the application be upgraded and processed as a Type II variation.

For the purpose of this Annex 'test procedure' has the same meaning as 'analytical procedure'; 'limits' has the same meaning as 'acceptance criteria'. 'Specification parameter' means the quality attribute for which a test procedure and limits are set, e.g. assay, identity, water content. The addition or deletion of a specification parameter therefore includes its corresponding test method and limits.

When several minor changes are taking place (e.g. to the same method or process or material) at the same time or in cases of a major update of the quality information for the active substance or the finished product, the applicant should take into account the overall impact of these changes on the quality, safety or efficacy of the medicinal product when considering the appropriate classification and submit them accordingly.

Specific supporting data for Type IB and Type II variations will depend on the specific nature of the change.

Furthermore, if a variation leads to a revision of the summary of product characteristics, labelling or package leaflet (jointly referred to as 'the product information'), this change is considered part of that variation. In such cases updated product information has to be submitted as part of the application with the relevant translations. Mock-ups of the packaging should be provided to the competent authority (assessment organization) of the reference Member State or Member State concerned.

There is no need to notify the competent authorities of an updated monograph of the Pharmacopoeia of the Union or a pharmacopoeia of a Member State in the case that reference is made to the 'current edition' in the dossier of an authorized medicinal product. Applicants are reminded that compliance with the updated monograph should be implemented within 180 calendar days.

Therefore, Section D in this Annex provides a list of variations which are specific to such PMFs or VAMFs. Following review of these variations, any marketing authorization concerned must be updated in accordance with Section B.V of this Annex. In case the documentation of the human plasma used as starting material for a plasma derived medicinal product is not submitted as a PMF, variations to this starting material as described in the marketing authorization dossier should also be handled in accordance with this Annex.

References in this Annex to changes to the marketing authorization dossier mean addition, replacement or deletion, unless specifically indicated. If amendments to the dossier only concern editorial changes, such changes should generally not be submitted as a separate variation, but they can be included in a variation concerning that part of the dossier.

In such cases the changes should be clearly identified in the application form as editorial changes and a declaration that the content of the concerned part of the dossier has not been changed by the editorial changes beyond the scope of the variation submitted should be provided. It should be noted that editorial changes include the removal of obsolete or redundant text but not the removal of specification parameters or manufacturing descriptions.

A. ADMINISTRATIVE CHANGES

A.1 Change in the name and/or address of the marketing authorization holder	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1, 2	IA_{IN}
Conditions 1. The marketing authorization holder must remain the same legal entity.			
Documentation 1. A formal document from a relevant official body (e.g. Tax Service) in which the new name or new address is mentioned. 2. Revised product information.			
A.2 Change in the (invented) name of the medicinal product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Medicinal products authorized for marketing in accordance with the Rules of authorization and assessment of medicinal products for human use in the Eurasian Economic Union	1	1, 2	IA_{IN}
b) Nationally authorized medicinal products (only in the reference Member State)		2	IB
Conditions 1. The check by the reference Member State on the acceptability of the new name has been finalized and was positive.			
Documentation 1. Copy of the reference Member State letter of acceptance of the new (invented) name. 2. Revised product information.			
A.3 Change in name of the active substance or of an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1, 2	1, 2	IA_{IN}
Conditions 1. The active substance/excipient must remain the same.			
Documentation 1. Proof of acceptance by WHO or copy of the INN list. If applicable, proof that the change is in line with the Ph. Eur. For herbal medicinal product, declaration that the name is in accordance with the Union guidance. 2. Revised product information			
A.4 Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites); or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where	Conditions to be fulfilled	Documentation to be supplied	Procedure type

specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel excipient (where specified in the technical dossier)			
	1	1, 2, 3	IA

Conditions

1. The manufacturing site and all manufacturing operations must remain the same.

Documentation

1. A formal document from a relevant official body (e.g. Tax Service) in which the new name and/or address is mentioned.
2. Amendment of the relevant section(s) of the dossier.
3. In case of change in the name of the holder of the Active Substance Master File holder, updated 'letter of access'.

A.5 Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The activities for which the manufacturer/importer is responsible include batch release	1	1, 2	IA_{IN}
b) The activities for which the manufacturer/importer is responsible do not include batch release	1	1, 2	IA

Conditions

1. The manufacturing site undergoing the name and/or address change and all manufacturing operations must remain the same.

Documentation

1. Copy of the modified manufacturing authorization, if available; or a formal document from a relevant official body (e.g. Tax Service) in which the new name and/or address is mentioned.
2. If applicable, amendment of the relevant section(s) of the dossier, including revised product information as appropriate.

A.6 Change in ATC Code	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1, 2	IA

Conditions

1. Change following granting of or amendment to ATC Code by WHO.

Documentation

1. Proof of acceptance (by WHO) or copy of the ATC Code list.
2. Revised product information

A.7 Deletion of manufacturing sites for an active substance, intermediate or finished product, packaging site, manufacturer responsible for	Conditions to be fulfilled	Documentation to be supplied	Procedure type

batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)			
	1, 2	1, 2	IA

Conditions

1. There should at least remain one site/manufacturer, as previously authorized, performing the same function as the one(s) concerned by the deletion. Where applicable at least one manufacturer responsible for batch release that is able to certify the product testing for the purpose of batch release within the Union remains in the Union.
2. The deletion should not be due to critical deficiencies concerning manufacturing.

Documentation

1. The variation application form should clearly outline the 'present' and 'proposed' manufacturers as listed in section 2.5 of the application form for marketing authorizations.
2. Amendment of the relevant section(s) of the dossier, including revised product information as appropriate.

A.8 Changes to date of the audit to verify GMP compliance of the manufacturer of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			IA

Documentation

1. Written confirmation from the manufacturer of the finish product stating verification of compliance of the manufacturer of the active substance with the Rules of good manufacturing practices.

B. QUALITY CHANGES

B.I Active substance

B.I.a) *Manufacture*

B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	1, 2, 3	1, 2, 3, 4, 5, 6, 7	IA_{IN}
b) Introduction of a manufacturer of the active substance supported by an ASMF			II
c) The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physicochemical properties impacting on			II

bioavailability			
d) New manufacturer of material for which an assessment is required of viral safety and/or TSE risk			II
e) The change relates to a biological active substance or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product			II
f) Changes to quality control testing arrangements for the active substance-replacement or addition of a site where batch control/testing takes place	2, 4	1, 5	IA
g) Introduction of a new manufacturer of the active substance that is not supported by an ASMF and requires significant update to the relevant active substance section of the dossier			II
h) Addition of an alternative sterilization site for the active substance using a Pharmacopoeia of the Union method		1, 2, 4, 5, 8	IB
i) Introduction of a new site of micronization	2, 5	1, 4, 5, 6	IA
j) Changes to quality control testing arrangements for a biological active substance: replacement or addition of a site where batch control/testing including a biological/immunological/ immunochemical method takes place			II
k) New storage site of Master Cell Bank and/or Working Cell Banks		1, 5	IB

Conditions

1. For starting materials and reagents the specifications (including in process controls, methods of analysis of all materials), are identical to those already approved. For intermediates and active substances the specifications (including in process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved.
2. The active substance is not a biological/immunological substance or sterile.
3. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the Pharmacopoeia of the Union *on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.*
4. Method transfer from the old to the new site has been successfully completed.
5. The particle size specification of the active substance and the corresponding analytical method remain the same.

Documentation

1. Amendment of the relevant section(s) of the dossier, if applicable.
2. A declaration from the marketing authorisation holder or the ASMF holder, where applicable, that the synthetic route (or in case of herbal medicinal products, where appropriate the method of preparation, geographical source, production of herbal drug and

manufacturing route) quality control procedures and specifications of the active substance and of the starting material/reagent/intermediate in the manufacturing process of the active substance (if applicable) are the same as those already approved.

3. Either a TSE Ph. Eur. Certificate of Suitability for any new source of material or, where applicable, documentary evidence that the specific source of the TSE risk material has previously been assessed by the competent authority and shown to comply with the Pharmacopoeia of the Union *on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*. The information should include the following: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance.
4. Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the active substance from the current and proposed manufacturers/sites.
5. The variation application form should clearly outline the 'present' and 'proposed' manufacturers as listed in section 2.5 of the application form for marketing authorization.
6. A declaration by the Qualified Person (QP) of each of the manufacturing authorization holders listed in the application where the active substance is used as a starting material and a declaration by the Qualified Person (QP) of each of the manufacturing authorization holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances — see the note under variation No B.II.b.1.
7. Where relevant, a commitment of the manufacturer of the active substance to inform the MA holder of any changes to the manufacturing process, specifications and test procedures of the active substance.
8. Proof that the proposed site is appropriately authorized for the pharmaceutical form or product or manufacturing operation concerned‹o

B.I.a.2 Changes in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor change in the manufacturing process of the active substance	1, 2, 3, 4, 5, 6, 7	1, 2, 3	IA
b) Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product			II
c) The change refers to a biological/immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological substance, which may have a significant impact on the quality, safety and efficacy of the medicinal product and is not related to a protocol			II
d) The change relates to a herbal medicinal product and there is a change to any of the following: geographical source, manufacturing route or production			II

e) Minor change to the restricted part of an Active Substance Master File		1, 2, 3, 4	IB
Conditions 1. No adverse change in qualitative and quantitative impurity profile or in physicochemical properties. 2. The synthetic route remains the same, i.e. intermediates remain the same and there are no new reagents, catalysts or solvents used in the process. In the case of herbal medicinal products, the geographical source, production of the herbal substance and the manufacturing route remain the same. 3. The specifications of the active substance or intermediates are unchanged. 4. The change is fully described in the open ('applicant's') part of an Active Substance Master File, if applicable. 5. The active substance is not a biological/immunological substance. 6. The change does not refer to the geographical source, manufacturing route or production of a herbal medicinal product. 7. The change does not refer to the restricted part of an Active Substance Master File.			
Documentation 1. Amendment of the relevant section(s) of the dossier, and of the approved Active Substance Master File (where applicable), including a direct comparison of the present process and the new process. 2. Batch analysis data (in comparative tabular format) of at least two batches (minimum pilot scale) manufactured according to the currently approved and proposed process. 3. Copy of approved specifications of the active substance. 4. A declaration from the marketing authorization holder or the ASMF Holder, where applicable, that there is no change in qualitative and quantitative impurity profile or in physicochemical properties, that the synthetic route remains the same and that the specifications of the active substance or intermediates are unchanged.			
Note: for chemical active substances, this refers to substantial changes to the synthetic route or manufacturing conditions which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physicochemical properties impacting on bioavailability.			
B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Up to 10-fold increase compared to the originally approved batch size	1, 2, 3, 4, 6, 7, 8	1, 2, 5	IA
b) Downscaling down to 10-fold	1, 2, 3, 4, 5	1, 2, 5	IA
c) The change requires assessment of the comparability of a biological/immunological active substance			II
d) More than 10-fold increase compared to the originally approved batch size		1, 2, 3, 4	IB

e) The scale for a biological/immunological active substance is increased/decreased without process change (e.g. duplication of line)		1, 2, 3, 4	IB

Conditions

1. Any changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment.
2. Test results of at least two batches according to the specifications should be available for the proposed batch size.
3. The product concerned is not a biological/immunological medicinal product.
4. The change does not adversely affect the reproducibility of the process.
5. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
6. The specifications of the active substance/intermediates remain the same.
7. The active substance is not sterile.
8. The batch size is within the 10-fold range of the batch size foreseen when the marketing authorization was granted or following a subsequent change not agreed as a Type IA variation.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. The batch numbers of the tested batches having the proposed batch size.
3. Batch analysis data (in a comparative tabulated format) on a minimum of one production batch of the active substance or intermediate as appropriate, manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorization holder if outside specification (with proposed action).
4. Copy of approved specifications of the active substance (and of the intermediate, if applicable).

5 A declaration from the marketing authorization holder or the ASMF holder as appropriate that the changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during manufacture or because of stability concerns and that the specifications of the active substance/intermediates remain the same.

B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of in-process limits	1, 2, 3, 4	1, 2	IA
b) Addition of a new in-process test and limits	1, 2, 5, 6	1, 2, 3, 4, 6	IA
c) Deletion of a non-significant in-process test	1, 2, 7	1, 2, 5	IA
d) Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the active substance			II
e) Deletion of an in-process test which may have a significant effect on the overall quality of the			II

active substance			
f) Addition or replacement of an in-process test as a result of a safety or quality issue		1, 2, 3, 4, 6	IB

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).
7. The specification parameter does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any request for changing the frequency of testing.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Comparative table of current and proposed in-process tests.
3. Details of any new non-pharmacopoeial analytical method and validation data, where relevant.
4. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the active substance for all specification parameters.
5. Justification/risk assessment from the marketing authorization holder or the ASMF Holder, as appropriate, that the in-process tests are non-significant, or that the in-process tests are obsolete.
6. Justification from the MAH or ASMF Holder as appropriate for the new in-process test and limits.

B.I.a.5 Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Replacement of the strain(s) in a seasonal, pre-pandemic or a pandemic vaccine against human influenza			II

B.I.b) ***Quality Control of active substance***

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of specification limits for medicinal	1, 2, 3, 4	1, 2	IA_{IN}

products subject to Official Control Authority Batch Release			
b) Tightening of specification limits	1, 2, 3, 4	1, 2	IA
c) Addition of a new specification parameter to the specification with its corresponding test method	1, 2, 5, 6, 7	1, 2, 3, 4, 5, 7	IA
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	1, 2, 8	1, 2, 6	IA
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product			II
f) Change outside the approved specifications limits range for the active substance			II
g) Widening of the approved specifications limits for starting materials/intermediates, which may have a significant effect on the overall quality of the active substance and/or the finished product			II
h) Addition or replacement (excluding biological or immunological substance) of a specification parameter with its corresponding test method as a result of a safety or quality issue		1, 2, 3, 4, 5, 7	IB
i) Where there is no monograph in the Pharmacopoeia of the Union or the pharmacopoeia of a Member State for the active substance, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country		1, 2, 3, 4, 5, 7	IB

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeia microbiological methods).
7. For any material, the change does not concern a genotoxic impurity. If it involves the final active substance, other than for residual solvents which must be in line with the Pharmacopoeia of the Union limits, any new impurity control should be in line with the Pharmacopoeia of the Union or Pharmacopoeia of a Member State.
8. The specification parameter does not concern a critical parameter, for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the

manufacture of the active substance), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any request for skip testing.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical method and validation data, where relevant.
4. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the relevant substance for all specification parameters.
5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.
6. Justification/risk assessment from the marketing authorization holder or the ASMF Holder, as appropriate, that the in-process parameter is non-significant, or that the in-process parameter is obsolete.
7. Justification from the MAH or ASMF Holder as appropriate of the new specification parameter and the limits.

B.I.b.2 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor changes to an approved test procedure	1, 2, 3, 4	1, 2	IA
b) Deletion of a test procedure for the active substance or a starting material/reagent/intermediate, if an alternative test procedure is already authorized.	7	1	IA
c) Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance	1, 2, 3, 5, 6	1, 2	IA
d) Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological active substance			II
e) Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate		1, 2	IB

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.
2. There have been no changes of the total impurity limits; no new unqualified impurities are detected.
3. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).

4. The test method is not a biological/immunological/immunochemical method, or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The active substance is not biological/immunological.
7 An alternative test procedure is already authorized for the specification parameter and this procedure has not been added through IA/IA($_{IN}$) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier, including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).
2. Comparative validation results, or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.I.c) ***Container closure system***

B.I.c.1 Change in immediate packaging of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Qualitative and/or quantitative composition	1, 2, 3	1, 2, 3, 4, 6	IA
b) Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances			II
c) Liquid active substances (non-sterile)		1, 2, 3, 5, 6	IB

Conditions

1. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.
2 Relevant stability studies have been started under the Union guidance conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least 3 months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging, the 3 months' stability data do not yet have to be available. These studies must be finalized and the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the shelf-life/retest period (with proposed action).
3 Sterile, liquid and biological/immunological active substances are excluded.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Appropriate data on the new packaging (e.g. comparative data on permeability, e.g. for O_2, CO_2 moisture), including a confirmation that the material complies with relevant pharmacopoeial requirements or legislation of the Union on plastic materials and objects in contact with foodstuffs.
3. Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeia requirements or legislation of the

Union on plastic material and objects in contact with foodstuffs.

4. A declaration from the marketing authorization holder or the ASMF holder as appropriate that the required stability studies have been started under the Union guidance conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalized and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
5. The results of stability studies that have been carried out under the Union guidance conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalized, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved retest period (with proposed action).
6. Comparison of the current and proposed immediate packaging specifications, if applicable.

B.I.c.2 Change in the specification parameters and/or limits of the immediate packaging of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of specification limits	1, 2, 3, 4	1, 2	IA
b) Addition of a new specification parameter to the specification with its corresponding test method	1, 2, 5	1, 2, 3, 4, 6	IA
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	1, 2	1, 2, 5	IA
d) Addition or replacement of a specification parameter as a result of a safety or quality issue		1, 2, 3, 4, 6	IB

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a type II variation procedure) unless it has been previously assessed and agreed as part of a follow-up measure.
2. The change does not result from unexpected events arising during manufacture of the packaging material or during storage of the active substance.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical method and validation data, where relevant.
4. Batch analysis data on two batches of the immediate packaging for all specification

parameters.

5 Justification/risk assessment from the marketing authorization holder or the ASMF Holder, as appropriate, that the in-process parameter is non-significant, or that the in-process parameter is obsolete.

6. Justification from the marketing authorization holder or the ASMF Holder, as appropriate, of the new specification parameter and the limits.

B.I.c.3 Change in test procedure for the immediate packaging of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor changes to an approved test procedure	1, 2, 3,	1, 2	IA
b) Other changes to a test procedure (including replacement or addition)	1, 3, 4	1, 2	IA
c) Deletion of a test procedure if an alternative test procedure is already authorized	5	1	IA

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.
2. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
4. The active substance/finished product is not biological/immunological.
5. There is still a test procedure registered for the specification parameter and this procedure has not been added through a IA/IA($_{IN}$) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier, including a description of the analytical methodology, a summary of validation data.
2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.I.d) ***Stability***

B.I.d.1 Change in the retest period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Retest period/storage period			
1. Reduction	1	1, 2, 3	IA
2. Extension of the retest period based on extrapolation of stability data not in accordance with The Union guidance (3)			II

3. Extension of storage period of a biological/immunological active substance not in accordance with an approved stability protocol			II
4. Extension or introduction of a retest period/storage period supported by real time data		1, 2, 3	IB

b) Storage conditions

1. Change to more restrictive storage conditions of the active substance	1	1, 2, 3	IA
2. Change in storage conditions of biological/immunological active substances, when the stability studies have not been performed in accordance with a currently approved stability protocol			II
3. Change in storage conditions of the active substance		1, 2, 3	IB
c) Change to an approved stability protocol	1, 2	1, 4	IA

Conditions

1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
2. The changes do not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.

Documentation

1. Amendment of the relevant section(s) of the dossier. This must contain results of appropriate real time stability studies, conducted in accordance with the relevant stability guidelines on at least two (three for biological medicinal products) pilot or production scale batches of the active substance in the authorized packaging material and covering the duration of the requested retest period or requested storage conditions.
2. Confirmation that stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.
3. Copy of approved specifications of the active substance.
4. Justification for the proposed changes.

B.I.e) ***Design Space and post-approval change management protocols***

B.I.e.1 Introduction of a new design space or extension of an approved design space for the active substance, concerning:	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) One unit operation in the manufacturing process of the active substance including the resulting in-process controls and/or test procedures		1, 2, 3	II
b) Test procedures for starting materials/reagents/intermediates and/or the active substance		1, 2, 3	II

Documentation

1. The design space has been developed in accordance with the relevant Union and international scientific guidelines. Results from product, process and analytical development studies (e.g. interaction of the different parameters forming the design space have to be studied, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the active substance has been achieved.
2. Description of the Design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.
3. Amendment of the relevant section(s) of the dossier.

B.I.e.2 Introduction of a post approval change management protocol related to the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2, 3	II

Documentation

1. Detailed description for the proposed change.
2. Change management protocol related to the active substance.
3. Amendment of the relevant section(s) of the dossier.

B.I.e.3 Deletion of an approved change management protocol related to the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1, 2	IA_{IN}

Conditions

1. The deletion of the approved change management protocol related to the active substance is not a result of unexpected events or out of specification results during the implementation of the change(s) described in the protocol and does not have any effect on the already approved information in the dossier.

Documentation

1. Justification for the proposed deletion.
2. Amendment of the relevant section(s) of the dossier.

B.I.e.4 Changes to an approved change management protocol	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Major changes to an approved change management protocol			II
b) Minor changes to an approved change management protocol that do not change the strategy defined in the protocol		1	IB

Documentation

1. Declaration that any change should be within the range of currently approved limits. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.

B.I.e.5 Implementation of changes foreseen in an approved change management protocol	Conditions to be fulfilled	Documentation to be supplied	Procedure type

a) The implementation of the change requires no further supportive data	1	1, 2, 4	IA_{IN}
b) The implementation of the change requires further supportive data		1, 2, 3, 4	IB
c) Implementation of a change for a biological/immunological medicinal product		1, 2, 3, 4, 5	IB
Conditions 1. The proposed change has been performed fully in line with the approved change management protocol.			
Documentation 1. Reference to the approved change management protocol. 2. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products. 3. Results of the studies performed in accordance with the approved change management protocol. 4. Amendment of the relevant section(s) of the dossier. 5. Copy of approved specifications of the active substance.			

B.II. FINISHED MEDICINAL PRODUCT

B.II.a) ***Description and composition***

B.II.a.1 Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Changes in imprints, bossing or other markings	1, 2, 3, 4	1, 2	IA_{IN}
b) Changes in scoring/break lines intended to divide into equal doses		1, 2, 3	IB
Conditions 1. Finished product release and end of shelf life specifications have not been changed (except for appearance). 2. Any ink must comply with the relevant pharmaceutical legislation. 3. The scoring/break lines are not intended to divide into equal doses. 4. Any product markings used to differentiate strengths should not be completely deleted.			
Documentation 1. Amendment of the relevant section(s) of the dossier, including a detailed drawing or written description of the current and new appearance, and including revised product information as appropriate. 2. Samples of the finished product where applicable. 3 Results of the appropriate Pharmacopoeia of the Union tests demonstrating equivalence in characteristics/correct dosing.			
B.II.a.2 Change in the shape or dimensions of	Conditions to	Documentation to	Procedure

the pharmaceutical form	be fulfilled	be supplied	type
a) Immediate release tablets, capsules, suppositories and pessaries	1, 2, 3, 4	1, 4	IA_{IN}
b) Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses		1, 2, 3, 4, 5	IB
c) Addition of a new kit for a radiopharmaceutical preparation with another fill volume			II
Conditions 1. If appropriate, the dissolution profile of the reformulated product is comparable to the old one. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the new product compared to the old one. 2. Release and end of shelf-life specifications of the product have not been changed (except for dimensions). 3. The qualitative or quantitative composition and mean mass remain unchanged. 4. The change does not relate to a scored tablet that is intended to be divided into equal doses.			
Documentation 1. Amendment of the relevant section(s) of the dossier, including a detailed drawing of the current and proposed situation, and including revised product information as appropriate. 2. Comparative dissolution data on at least one pilot batch of the current and proposed dimensions (no significant differences regarding comparability see the Rules of conducting bioequivalence studies of medicinal products in the Eurasian Economic Union (hereinafter referred to as the Rules of conducting bioequivalence studies)). For herbal medicinal product comparative disintegration data may be acceptable. 3. Justification for not submitting a new bioequivalence study according to the Rules of conducting bioequivalence studies. 4. Samples of the finished product where applicable. 5. Results of the appropriate Pharmacopoeia of the Union tests demonstrating equivalence in characteristics/correct dosing.			
Note: for B.II.a.2.c), applicants are reminded that any change to the 'strength' of the medicinal product requires the submission of an Extension application.			

B.II.a.3 Changes in the composition (excipients) of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Changes in components of the flavoring or coloring system			
1. Addition, deletion or replacement	1, 2, 3, 4, 5, 6, 7, 9, 11	1, 2, 4, 5, 6	IA_{IN}
2. Increase or reduction	1, 2, 3, 4, 11	1, 2, 4	IA
3. Biological veterinary medicinal products for oral use for which the coloring or flavoring agent is important for the uptake by target animal species			II

b) Other excipients

1. Any minor adjustment of the quantitative composition of the finished product with respect to excipients	1, 2, 4, 8, 9, 10	1, 2, 7	IA
2. Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product			II
3. Change that relates to a biological/immunological product			II
4. Any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk			II
5. Change that is supported by a bioequivalence study			II
6. Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level		1, 3, 4, 5, 6, 7, 8, 9	IB

Conditions

1. No change in functional characteristics of the pharmaceutical form, e.g. disintegration time, dissolution profile.
2. Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the finished product formulation.
3. The finished product specification has only been updated in respect of appearance/odor/taste and if relevant, deletion of an identification test.
4. Stability studies have been started under the Union guidance conditions (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least 3 months satisfactory stability data are at the disposal of the applicant (at time of implementation for Type IAs and at time of notification for Type IBs) and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalized and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action). In addition, where relevant, photo-stability testing should be performed.
5. Any new proposed components must comply with the relevant Union documents related to colors for use in foodstuffs and to flavors).
6. Any new component does not include the use of materials of human or animal origin for which assessment is required of viral safety data or compliance with the Pharmacopoeia of the Union *on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*.
7. Where applicable, the change does not affect the differentiation between strengths and does not have a negative impact on taste acceptability for paediatric formulations.
8. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one (no significant differences regarding comparability, see the Rules of conducting bioequivalence studies). For herbal medicinal products where

dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.

9. The change is not the result of stability issues and/or should not result in potential safety concerns, i.e. differentiation between strengths.
10. The product concerned is not a biological/immunological medicinal product.
11. For veterinary medicinal products for oral use, the change does not affect the uptake by target animal species.

Documentation

1. Amendment of the relevant section(s) of the dossier, including identification method for any new colorant, where relevant, and including revised product information as appropriate.
2. A declaration that the required stability studies have been started under the Union guidance conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalized and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
3. The results of stability studies that have been carried out under the Union guidance conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalized, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
4. Sample of the new product, where applicable.
5. Either a Ph. Eur. Certificate of Suitability for any new component of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by the competent authority and shown to comply with the scope of the Pharmacopoeia of the Union *on Minimising the Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products*. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.
6. Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate.

7 Justification for the change/choice of excipients etc. must be given by appropriate development pharmaceutics (including stability aspects and antimicrobial preservation where appropriate).

8. For solid dosage forms, comparative dissolution profile data of at least two pilot scale batches of the finished product in the new and old composition. For herbal medicinal products, comparative disintegration data may be acceptable.
9. Justification for not submitting a new bioequivalence study according to the Rules of conducting bioequivalence studies of the Union.

B.II.a.4 Change in coating weight of oral dosage forms or change in weight of capsule shells	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Solid oral pharmaceutical forms	1, 2, 3, 4	1, 2	IA
b) Gastro-resistant, modified or prolonged			II

release pharmaceutical forms where the coating is a critical factor for the release mechanism			

Conditions

1. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one. For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.
2. The coating is not a critical factor for the release mechanism.
3. The finished product specification has only been updated in respect of weight and dimensions, if applicable.
4. Stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least 3 months satisfactory stability data are at the disposal of the applicant at the time of implementation and assurance that these studies will be finalized. Data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. A declaration that the required stability studies have been started under the Union guidance conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalized and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). In addition, where relevant, photo-stability testing should be performed.

B.II.a.5 Change in concentration of a single-dose, total use parenteral product, where the amount of active substance per unit dose (i.e. the strength) remains the same	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II
B.II.a.6 Deletion of the solvent/diluent container from the pack	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2	IB

Documentation

1. Justification for the deletion, including a statement regarding alternative means to obtain the solvent/diluent as required for the safe and effective use of the medicinal product.
2. Revised product information.

B.II.b) ***Manufacture***

B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type

a) Secondary packaging site	1, 2	1,3, 8	IA_{IN}
b) Primary packaging site	1, 2, 3, 4, 5	1, 2, 3, 4, 8, 9	IA_{IN}
c) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/ immunological medicinal products, or for pharmaceutical forms manufactured by complex manufacturing processes			II
d) Site which requires an initial or product specific inspection			II
e) Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products		1, 2, 3, 4, 5, 6, 7, 8, 9	IB
f) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/immunological medicinal products		1, 2, 3, 4, 5, 6, 7, 8	IB

Conditions

1. Satisfactory inspection in the last 3 years by an inspection service of one of the Member States or of a country where an operational Good Manufacturing Practice (GMP) mutual recognition agreement (MRA) exists.
2. Site appropriately authorized (to manufacture the pharmaceutical form or product concerned).
3. Product concerned is not a sterile product.
4. Where relevant, for instance for suspensions and emulsions, validation scheme is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches.
5. Product concerned is not a biological/immunological medicinal product.

Documentation

1. Proof that the proposed site is appropriately authorized for the pharmaceutical form or product concerned.
2. Where relevant, the batch numbers, corresponding batch size and the manufacturing date of batches (≥ 3) used in the validation study should be indicated and the validation data presented, or validation protocol (scheme) to be submitted.
3. The variation application form should clearly outline the ‘present’ and ‘proposed’ finished product manufacturers as listed in section 2.5 of the application form.
4. Copy of approved release and end-of-shelf life specifications if relevant.
5. Batch analysis data on one production batch and two pilot-scale batches simulating the production process (or two production batches) and comparative data on the last three batches from the previous site; batch data on the next two production batches should be

available on request or reported if outside specifications (with proposed action).

6. For semisolid and liquid formulations in which the active substance is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology or any other appropriate imaging technique.
7. If the new manufacturing site uses the active substance as a starting material — A declaration by the Qualified Person (QP) at the site responsible for batch release that the active substance is manufactured in accordance with the Rules on good manufacturing practice for starting materials as adopted by the Union.
8. Amendment of the relevant section(s) of the dossier.
9. If the manufacturing site and the primary packaging site are different, conditions of transport and bulk storage should be specified and validated.

Notes:

In case of a change in or a new manufacturing site in a country outside the Union without an operational GMP mutual recognition agreement with the Union, marketing authorization holders are advised to consult the relevant competent authorities first before making the submission of the notification and to provide information about any previous Union inspection in the last 2-3 years and/or any planned Union inspection(s) including inspection dates, product category inspected, Supervisory Authority and other relevant information. This will facilitate the arrangement for a EAEU GMP inspection by an inspection service of one of the Member States if needed.

QP Declarations in relation to active substances

Manufacturing authorization holders are obliged to only use as starting materials active substances that have been manufactured in accordance with GMP so a declaration is expected from each of the manufacturing authorization holders that use the active substance as a starting material. In addition, as the QP responsible for batch certification takes overall responsibility for each batch, a further declaration from the QP responsible for batch certification is expected when the batch release site is a different site from the above.

In many cases only one manufacturing authorization holder is involved and therefore only one declaration will be required. However, when more than one manufacturing authorization holder is involved rather than provide multiple declarations it may be acceptable to provide a single declaration signed by one QP. This will be accepted provided that:

The declaration makes it clear that it is signed on behalf of all the involved QPs.

The arrangements are underpinned by a technical agreement as described in Chapter 7 of the Rules of GMP and the QP providing the declaration is the one identified in the agreement as taking specific responsibility for the GMP compliance of the active substance manufacturer(s).

Note: these arrangements are subject to inspection by the competent authorities.

B.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Replacement or addition of a site where batch control/testing takes place	2, 3, 4, 5	1, 2, 4	IA
b) Replacement or addition of a site where batch control/testing takes place for a biological/immunological product and any of the test methods performed at the site is a biological/immunological method			II
c) Replacement or addition of a manufacturer responsible for importation and/or batch release			
1. Not including batch control/testing	1, 2,5	1, 2, 3, 4	IA_{IN}

2. Including batch control/testing	1, 2, 3, 4, 5	1, 2, 3, 4	IA_{IN}
3. Including batch control/testing for a biological/immunological product and any of the test methods performed at that site is a biological/immunological/immunochemical method			II

Conditions

1. The manufacturer responsible for batch release must be located within the Union. At least one batch release site remains within the Union that is able to certify the product testing for the purpose of batch release within the Union.
2. The site is appropriately authorized.
3. The product is not a biological/immunological medicinal product.
4. Method transfer from the old to the new site or new test laboratory has been successfully completed.
5. At least one batch control/testing site remains within the Union or in a country where an operational and suitably scoped GMP mutual recognition agreement (MRA) exists between the country concerned and the Union, that is able to carry out product testing for the purpose of batch release within the Union.

Documentation

1. Attach copy of manufacturing authorization(s) or where no manufacturing authorization exists a certificate of GMP compliance issued within the last 3 years by the relevant competent authority.
2. The variation application form should clearly outline the 'present' and 'proposed' finished product manufacturers, importer, batch control/testing and batch release sites as listed in section 2.5 of the application form for marketing authorization.
3. A declaration by the Qualified Person (QP) responsible for batch certification stating that the active substance manufacturer(s) referred to in the marketing authorization operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances — see the note under variation No B.II.b.1.

4 Amendment of the relevant section(s) of the dossier, including revised product information as appropriate.

B.II.b.3 Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor change in the manufacturing process	1, 2, 3, 4, 5, 6, 7	1, 2, 3, 4, 5, 6, 7, 8	IA
b) Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product			II
c) The product is a biological/immunological medicinal product and the change requires an assessment of comparability			II

d) Introduction of a non-standard terminal sterilization method			II
e) Introduction or increase in the overage that is used for the active substance			II
f) Minor change in the manufacturing process of an aqueous oral suspension		1, 2, 4, 6, 7,8	IB

Conditions

1. No change in qualitative and quantitative impurity profile or in physicochemical properties.
2. Either the change relates to an immediate release solid oral dosage form/oral solution and the medicinal product concerned is not a biological/immunological or herbal medicinal product; or the change relates to process parameter(s) that, in the context of a previous assessment, have been considered to have no impact on the quality of the finished product (regardless of the type of product and/or dosage form).
3. The manufacturing principle including the single manufacturing steps remain the same, e.g. processing intermediates and there are no changes to any manufacturing solvent used in the process.
4 The currently registered process has to be controlled by relevant in-process controls and no changes (widening or deletion of limits) are required to these controls.
5. The specifications of the finished product or intermediates are unchanged.
6. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.
7. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batch and at least 3 months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1. Amendment of the relevant section(s) of the dossier, including a direct comparison of the present process and the new process.
2. For semi-solid and liquid products in which the active substance is present in non-dissolved form: appropriate validation of the change including microscopic imaging of particles to check for visible changes in morphology; comparative size distribution data by an appropriate method.
3. For solid dosage forms: dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside specification (with proposed action). For herbal medicinal products, comparative disintegration data may be acceptable.
4. Justification for not submitting a new bioequivalence study according to the Rules of conducting bioequivalence studies.
5. For changes to process parameter(s) that have been considered to have no impact on the quality of the finished product, declaration to this effect reached in the context of the previously approved risk assessment.
6. Copy of approved release and end-of-shelf life specifications.
7. Batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured to both the currently approved and the proposed process. Batch data on the next two full production batches should be made available upon request and reported by the

marketing authorization holder if outside specification (with proposed action).

8. Declaration that relevant stability studies have been started under the Union guidance conditions, as appropriate, (with indication of the batch numbers concerned) and relevant stability parameters have been assessed in at least one pilot scale or industrial scale batch and at least 3 months satisfactory stability data are at the disposal of the applicant at time of notification and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalized and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

B.II.b.4 Change in the batch size (including batch size ranges) of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Up to 10-fold compared to the originally approved batch size	1, 2, 3, 4, 5, 7	1, 4	IA
b) Downscaling down to 10-fold	1, 2, 3, 4, 5, 6	1, 4	IA
c) The change requires assessment of the comparability of a biological/immunological medicinal product or the change in batch size requires a new bioequivalence study			II
d) The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes			II
e) More than 10-fold increase compared to the originally approved batch size for immediate release (oral) pharmaceutical forms		1, 2, 3, 4, 5, 6	IB
f) The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)		1, 2, 3, 4, 5, 6	IB

Conditions

1. The change does not affect reproducibility and/or consistency of the product.
2. The change relates to conventional immediate release oral pharmaceutical forms or to non-sterile liquid based pharmaceutical forms.
3. Any changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch-size, e.g. use of different sized equipment.
4. Validation scheme is available or validation of the manufacture has been successfully carried out according to the current protocol with at least three batches at the proposed new batch size in accordance with the relevant guidelines.
5. The product concerned is not a biological/immunological medicinal product.
6. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
7. The batch size is within the 10-fold range of the batch size foreseen when the marketing authorization was granted or following a subsequent change not agreed as a Type IA variation.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Batch analysis data (in a comparative tabulated format) on a minimum of one production batch manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the MAH if outside specifications (with proposed action).
3. Copy of approved release and end-of-shelf life specifications.
4. Where relevant the batch numbers, corresponding batch size and the manufacturing date of batches (≥ 3) used in the validation study should be indicated or validation protocol (scheme) be submitted.
5. The validation results should be provided
6. The results of stability studies that have been carried out under the Union guidance conditions, on the relevant stability parameters, on at least one pilot or industrial scale batch, covering a minimum period of 3 months, and an assurance is given that these studies will be finalized, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). For biologicals/immunologicals: a declaration that an assessment of comparability is not required.

B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of in-process limits	1, 2, 3, 4	1, 2	IA
b) Addition of a new test(s) and limits	1, 2, 5, 6	1, 2, 3, 4, 5, 7	IA
c) Deletion of a non-significant in-process test	1, 2, 7	1, 2, 6	IA
d) Deletion of an in-process test which may have a significant effect on the overall quality of the finished product			II
e) Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product			II
f) Addition or replacement of an in-process test as a result of a safety or quality issue		1, 2, 3, 4, 5, 7	IB

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).

7. The in-process test does not concern the control of a critical parameter, e.g.: assay, impurities (unless a particular solvent is definitely not used in the manufacture) any critical physical characteristics (particle size, bulk, tapped density, etc.) identity test (unless there is a suitable alternative control already present) microbiological control (unless not required for the particular dosage form)
Documentation 1. Amendment of the relevant section(s) of the dossier. 2. Comparative table of current and proposed in-process tests and limits. 3. Details of any new analytical method and validation data, where relevant. 4. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters. 5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch manufactured using the current and new in-process tests. For herbal medicinal products, comparative disintegration data may be acceptable. 6 Justification/risk assessment showing that the in-process test is non-significant or that it is obsolete. 7. Justification of the new in-process test and limits.

B.II.c) ***Control of excipients***

B.II.c.1 Change in the specification parameters and/or limits of an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of specification limits	1, 2, 3, 4	1, 2	IA
b) Addition of a new specification parameter to the specification with its corresponding test method	1, 2, 5, 6, 7	1, 2, 3, 4, 6, 8	IA
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	1, 2, 8	1, 2, 7	IA
d) Change outside the approved specifications limits range			II
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product			II
f) Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method, as a result of a safety or quality issue		1, 2, 3, 4, 5, 6, 8	IB
g) Where there is no monograph in the Pharmacopoeia of the Union or the pharmacopoeia of a Member State for the excipient, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country		1, 2, 3, 4, 5, 6, 8	IB

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The test method is not a biological/immunological/immunochemical method, or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods)
7. The change does not concern a genotoxic impurity.
8. The specification parameter does not concern the control of a critical parameter, e.g.:

   impurities (unless a particular solvent is definitely not used in the manufacture of the excipient)

   any critical physical characteristics (particle size, bulk, tapped density, etc.)

   identity test (unless there is a suitable alternative control already present)

   microbiological control (unless not required for the particular dosage form)

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical method and validation data, where relevant.
4. Batch analysis data on two production batches (3 production batches for biological excipients) of the excipient for all specification parameters.
5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the excipient complying with the current and proposed specification. For herbal medicinal products comparative disintegration data may be acceptable.
6. Justification for not submitting a new bioequivalence study according to the Rules of conducting bioequivalence studies of the Union, if appropriate.
7. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.
8. Justification of the new specification parameter and the limits.

B.II.c.2 Change in test procedure for an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor changes to an approved test procedure	1, 2, 3, 4	1, 2	IA
b) Deletion of a test procedure if an alternative test procedure is already authorized	5	1	IA
c) Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent			II

d) Other changes to a test procedure (including replacement or addition)		1, 2	IB

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.
2. There have been no changes of the total impurity limits; no new unqualified impurities are detected.
3. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
4. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).
5. An alternative test procedure is already authorized for the specification parameter and this procedure has not been added through IA/IA(IN) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier, including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).
2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.II.c.3 Change in source of an excipient or reagent with TSE risk	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) From TSE risk material to vegetable or synthetic origin			
1. For excipients or reagents not used in the manufacture of a biological/immunological active substance or in a biological/immunological medicinal product	1	1	IA
2. For excipients or reagents used in the manufacture of a biological/immunological active substance or in a biological/immunological medicinal product		1, 2	IB
b) Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by a TSE certificate of suitability			II

Conditions

1. Excipient and finished product release and end of shelf life specifications remain the same.

Documentation

1. Declaration from the manufacturer or the marketing authorization holder of the material that it is purely of vegetable or synthetic origin.
2. Study of equivalence of the materials and the impact on production of the final material and impact on behavior (e.g. dissolution characteristics) of the finished product.

B.II.c.4 Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier) or a novel excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor change in synthesis or recovery of a non-pharmacopoeial excipient or a novel excipient	1, 2	1, 2, 3, 4	IA
b) The specifications are affected or there is a change in physicochemical properties of the excipient which may affect the quality of the finished product.			II
c) The excipient is a biological/immunological substance			II

Conditions

1. The synthetic route and specifications are identical and there is no change in qualitative and quantitative impurity profile (excluding residual solvents, provided they are controlled in accordance with Union guidance limits), or in physicochemical properties.
2. Adjuvants are excluded.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Batch analysis data (in a comparative tabulated format) of at least two batches (minimum pilot scale) of the excipient manufactured according to the old and the new process.
3. Where appropriate, comparative dissolution profile data for the finished product of at least two batches (minimum pilot scale). For herbal medicinal products, comparative disintegration data may be acceptable.
4. Copy of approved and new (if applicable) specifications of the excipient.

B.II.d) ***Control of finished product***

B.II.d.1 Change in the specification parameters and/or limits of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of specification limits	1, 2, 3, 4	1, 2	IA
b) Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release	1, 2, 3, 4	1, 2	IA_{IN}
c) Addition of a new specification parameter to the specification with its corresponding test method	1, 2, 5, 6, 7	1, 2, 3, 4, 5, 7	IA
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odor and taste or identification test for a coloring or flavoring material)	1, 2, 9	1, 2, 6	IA

e) Change outside the approved specifications limits range			II
f) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product			II
g) Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method as a result of a safety or quality issue		1, 2, 3, 4, 5, 7	IB
h) Update of the dossier to comply with the provisions of an updated general monograph of the Pharmacopoeia of the Union for the finished product ([8])	1, 2, 3, 4, 7, 8	1, 2	IA_{IN}
i) Pharmacopoeia of the Union 2.9.40 Uniformity of dosage units is introduced to replace the currently registered method, either Pharmacopoeia of the Union 2.9.5 (Uniformity of mass) or Pharmacopoeia of the Union 2.9.6 (Uniformity of content)	1, 2,10	1, 2, 4	IA

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a type II variation procedure), unless the supporting documentation has been already assessed and approved within another procedure.
2. The change does not result from unexpected events arising during manufacture, e.g. new unqualified impurity; change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance.
7. The change does not concern any impurities (including genotoxic) or dissolution.
8. The change concerns the updating of the microbial control limits to be in line with the current Pharmacopoeia, and the currently registered microbial control limits does not include any additional specified controls over the Pharmacopoeia requirements for the particular dosage form.
9. The specification parameter or proposal for the specific dosage form does not concern a critical parameter for example:

   assay,

impurities (unless a particular solvent is definitely not used in the manufacture of the finished product)

any critical physical characteristics (hardness or friability for uncoated tablets, dimensions, etc.)

any request for skip testing.

10. The proposed control is fully in line with the Table 2.9.40.-1 of Pharmacopoeia of the Union 2.9.40 monograph, and does not include the alternative proposal for testing uniformity of dosage units by Mass Variation instead of Content Uniformity when the latter is specified in Table 2.9.40.-1.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical method and validation data, where relevant.
4. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters
5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.

6 Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.

7. Justification of the new specification parameter and the limits

B.II.d.2 Change in test procedure for the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor changes to an approved test procedure	1, 2, 3, 4,	1,2	IA
b) Deletion of a test procedure if an alternative method is already authorized	4	1	IA
c) Substantial change to, or replacement of, a biological/immunological/immunochemical test method or a method using a biological reagent or replacement of a biological reference preparation not covered by an approved protocol			II
d) Other changes to a test procedure (including replacement or addition)		1, 2	IB
e) Update of the test procedure to comply with the updated general monograph in the Pharmacopoeia of the Union.	2, 3, 4, 5	1	IA

f) To reflect compliance with the Pharmacopoeia of the Union and remove reference to the outdated internal test method and test method number (9)	2, 3, 4, 5	1	IA
Conditions 1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure. 2. There have been no changes of the total impurity limits; no new unqualified impurities are detected 3. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method); 4. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods). 5. The registered test procedure already refers to the general monograph of the Pharmacopoeia of the Union and any changes are minor in nature and require update of the technical dossier.			
Documentation 1. Amendment of the relevant section(s) of the dossier, including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable). 2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent.; This requirement is not applicable in case of an addition of a new test procedure.			

B.II.d.3 Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II

B.II.e) ***Container closure system***

B.II.e.1 Change in immediate packaging of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Qualitative and quantitative composition			
1. Solid pharmaceutical forms	1, 2, 3	1, 2, 3, 4, 6	IA
2. Semi-solid and non-sterile liquid pharmaceutical forms		1, 2, 3, 5, 6	IB
3. Sterile medicinal products and biological/immunological medicinal products.			II

4. The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.			II

b) Change in type of container or addition of a new container

1. Solid, semi-solid and non-sterile liquid pharmaceutical forms		1, 2, 3, 5, 6, 7	IB
2. Sterile medicinal products and biological/immunological medicinal products			II
3. Deletion of an immediate packaging container that does not lead to the complete deletion of a strength or pharmaceutical form	4	1, 8	IA

Conditions

1. The change only concerns the same packaging/container type (e.g. blister to blister).
2. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.
3. Relevant stability studies have been started under the Union guidance conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least 3 months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging, e.g. thicker blister packaging, the 3 months' stability data do not yet have to be available. These studies must be finalized and the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
4. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.

Documentation

1. Amendment of the relevant section(s) of the dossier, including revised product information as appropriate.
2. Appropriate data on the new packaging (comparative data on permeability, e.g. for O_2, CO_2 moisture).
3. Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeial requirements or legislation of the Union on plastic material and objects in contact with foodstuffs.
4. A declaration that the required stability studies have been started under the Union guidance conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalized and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end

of the approved shelf life (with proposed action).

5. The results of stability studies that have been carried out under the Union guidance conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalized, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
6. Comparative table of the current and proposed immediate packaging specifications, if applicable.
7. Samples of the new container/closure where applicable.
8. Declaration that the remaining pack-size(s) is/are consistent with the dosage regimen and duration of treatment and adequate for the dosing instructions as approved in the summary of product characteristics.

Note: for B.II.e.1.b), applicants are reminded that any change which results in a 'new pharmaceutical form' requires the submission of an Extension application.

B.II.e.2 Change in the specification parameters and/or limits of the immediate packaging of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of specification limits	1, 2, 3, 4	1, 2	IA
b) Addition of a new specification parameter to the specification with its corresponding test method	1, 2, 5	1, 2, 3, 4, 6	IA
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	1, 2	1, 2, 5	IA
d) Addition or replacement of a specification parameter as a result of a safety or quality issue		1, 2, 3, 4, 6	IB

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorization application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical method and validation data, where relevant.
4. Batch analysis data on two batches of the immediate packaging for all specification parameters.
5. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.
6. Justification of the new specification parameter and the limits.

B.II.e.3 Change in test procedure for the immediate packaging of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor changes to an approved test procedure	1, 2, 3	1, 2	IA
b) Other changes to a test procedure (including replacement or addition)	1, 3, 4	1, 2	IA
c) Deletion of a test procedure if an alternative test procedure is already authorized	5	1	IA

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and validation studies show that the updated test procedure is at least equivalent to the former test procedure.
2. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
4. The active substance/finished product is not biological/immunological.
5. An alternative test procedure is already authorized for the specification parameter and this procedure has not been added through IA/IA(IN) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier, including a description of the analytical methodology, a summary of validation data.
2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging)	Conditions to be fulfilled	Documentation to be supplied	Procedure type

a) Non-sterile medicinal products	1, 2, 3	1, 2, 4	IA
b) The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product			II
c) Sterile medicinal products		1, 2, 3, 4	IB

Conditions

1. No change in the qualitative or quantitative composition of the container.
2. The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the finished product.
3. In case of a change in the headspace or a change in the surface/volume ratio, stability studies in accordance with the relevant guidelines have been started and relevant stability parameters have been assessed in at least two pilot scale (three for biological/immunological medicinal products) or industrial scale batches and at least 3 months (6 months for biological/immunological medicinal products) stability data are at the disposal of the applicant. Assurance is given that these studies will be finalized and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1. Amendment of the relevant section(s) of the dossier, including description, detailed drawing and composition of the container or closure material, and including revised product information as appropriate.
2. Samples of the new container/closure where applicable.
3. Revalidation studies have been performed in case of sterile products terminally sterilized. The batch numbers of the batches used in the revalidation studies should be indicated, where applicable.
4. In case of a change in the headspace or a change in the surface/volume ratio, a declaration that the required stability studies have been started under the Union guidance conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation for a Type IA notification and time of submission of a Type IB notification, and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalized and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

B.II.e.5 Change in pack size of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Change in the number of units (e.g. tablets, ampoules, etc.) in a pack			
1. Change within the range of the currently approved pack sizes	1, 2	1, 3	IA_{IN}
2. Change outside the range of the currently approved pack sizes		1, 2, 3	IB
b) Deletion of pack size(s)	3	1, 2	IA
c) Change in the fill weight/fill volume of sterile multi-dose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products			II
d) Change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) products		1, 2, 3	IB
Conditions 1. New pack size should be consistent with the posology and treatment duration as approved in the Summary of Product Characteristics. 2. The primary packaging material remains the same. 3. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the Summary of Product Characteristics.			
Documentation 1. Amendment of the relevant section(s) of the dossier including revised product information as appropriate. 2. Justification for the new/remaining pack-size, showing that the new/remaining size is/are consistent with the dosage regimen and duration of treatment as approved in the summary of product characteristics 3. Declaration that stability studies will be conducted in accordance with the relevant guidelines for products where stability parameters could be affected. Data to be reported only if outside specifications (with proposed action).			
Note: for B.II.e.5.c) and d), applicants are reminded that any changes to the 'strength' of the medicinal product require the submission of an Extension application.			
B.II.e.6 Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as color of flip-off caps, color code rings on ampoules, change of needle shield	Conditions to be fulfilled	Documentation to be supplied	Procedure type

(different plastic used))			
a) Change that affects the product information	1	1	IA_{IN}
b) Change that does not affect the product information	1	1	IA
Conditions 1. The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.			
Documentation 1. Amendment of the relevant section(s) of the dossier, including revised product information as appropriate.			
B.II.e.7 Change in supplier of packaging components or devices (when mentioned in the dossier)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Deletion of a supplier	1	1	IA
b) Replacement or addition of a supplier	1, 2, 3, 4	1, 2, 3	IA
c) Any change to suppliers of spacer devices for metered dose inhalers			II
Conditions 1. No deletion of packaging component or device. 2. The qualitative and quantitative composition of the packaging components/device and design specifications remain the same. 3. The specifications and quality control method are at least equivalent. 4. The sterilization method and conditions remain the same, if applicable.			
Documentation 1. Amendment of the relevant section(s) of the dossier. 2. For devices for medicinal products for human use, proof of Union marketing authorization for a medical device. 3. Comparative table of current and proposed specifications, if applicable.			

B.II.f) ***Stability***

B.II.f.1 Change in the shelf-life or storage conditions of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Reduction of the shelf life of the finished product			
1. As packaged for sale	1	1, 2, 3	IA_{IN}
2. After first opening	1	1, 2, 3	IA_{IN}
3. After dilution or reconstitution	1	1, 2, 3	IA_{IN}
b) Extension of the shelf life of the finished product			
1. As packaged for sale (supported by real time data)		1, 2, 3	IB
2. After first opening (supported by real time data)		1, 2, 3	IB
3. After dilution or reconstitution (supported by real time data)		1, 2, 3	IB
4. Extension of the shelf-life based on extrapolation of stability data not in accordance with The Union guidance (*)			II
5. Extension of the shelf-life of a biological/immunological medicinal product in accordance with an approved stability protocol.		1, 2, 3	IB
c) Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol			II
d) Change in storage conditions of the finished product or the diluted/reconstituted product		1, 2, 3	IB
e) Change to an approved stability protocol	1, 2	1, 4	IA
Conditions 1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns. 2. The change does not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.			
Documentation 1. Amendment of the relevant section(s) of the dossier. This must contain results of appropriate real time stability studies (covering the entire shelf life) conducted in accordance with the relevant stability guidelines on at least two pilot scale batches (1) of the finished product in the authorized packaging material and/or after first opening or reconstitution, as appropriate;			

where applicable, results of appropriate microbiological testing should be included.

2. Revised product information

3. Copy of approved end of shelf life finished product specification and where applicable, specifications after dilution/reconstitution or first opening.

4. Justification for the proposed change(s).

* Примечание	Note: extrapolation not applicable for biological/immunological medicinal product.
1	Pilot scale batches can be accepted with a commitment to verify the shelf life on production scale batches.

B.II.g) ***Design Space and post approval change management protocol***

B.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product, concerning:	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) One or more unit operations in the manufacturing process of the finished product including the resulting in-process controls and/or test procedures		1, 2, 3	II
b) Test procedures for excipients/intermediates and/or the finished product.		1, 2, 3	II

Documentation

1. Results from product and process development studies (including risk assessment and multivariate studies, as appropriate) demonstrating that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the finished product has been achieved.

2. Description of the design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.

3. Amendment of the relevant section(s) of the dossier.

B.II.g.2 Introduction of a post approval change management protocol related to the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2, 3	II

Documentation

1. Detailed description for the proposed change.

2. Change management protocol related to the finished product.

3. Amendment of the relevant section(s) of the dossier.

B.II.g.3 Deletion of an approved change management protocol related to the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1, 2	IA_{IN}

Conditions

1. The deletion of the approved change management protocol related to the finish product is not a result of unexpected events or out of specification results during the implementation of the change(s) described in the protocol and does not have any effect on the already approved information in the dossier.

Documentation

1. Justification for the proposed deletion.
2. Amendment of the relevant section(s) of the dossier.

B.II.g.4 Changes to an approved change management protocol	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Major changes to an approved change management protocol			II
b) Minor changes to an approved change management protocol that do not change the strategy defined in the protocol		1	IB

Documentation

1. Declaration that any change should be within the range of currently approved limits. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.

B.II.g.5 Implementation of changes foreseen in an approved change management protocol	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The implementation of the change requires no further supportive data	1	1, 2, 4	IA_{IN}
b) The implementation of the change requires further supportive data		1, 2, 3, 4	IB
c) Implementation of a change for a biological/immunological medicinal product		1, 2, 3, 4, 5	IB

Conditions

1. The proposed change has been performed fully in line with the approved change management protocol, which requires its immediate notification following implementation.

Documentation

1. Reference to the approved change management protocol.
2. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.
3. Results of the studies performed in accordance with the approved change management protocol.
4. Amendment of the relevant section(s) of the dossier.
5. Copy of approved specifications of the finished product.

B.II.h ***Adventitious Agents Safety***

B.II.h.1 Update to the 'Adventitious Agents Safety Evaluation' information (section 3.2.A.2)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Studies related to manufacturing steps investigated for the first time for one or more adventitious agents			II
b) Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier			
1) with modification of risk assessment			II
2) without modification of risk assessment		1, 2, 3	IB

Documentation

1. Amendment of the relevant section(s) of the dossiers including the introduction of the new studies to investigate the capability of manufacturing steps to inactivate/reduce adventitious agents.
2. Justification that the studies do not modify the risk assessment.
3. Amendment of product information (where applicable).

B.III CEP/TSE/MONOGRAPHS

B.III.1 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability:	Conditions to be fulfilled	Documentation to be supplied	Procedure type
For an active substance For a starting material/reagent/intermediate used in the manufacturing process of the active substance For an excipient			

a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.

1. New certificate from an already approved manufacturer	1, 2, 3, 4, 5, 6, 9	1, 2, 3, 4, 5	IA_{IN}
2. Updated certificate from an already approved manufacturer	1, 2, 3, 4, 6	1, 2, 3, 4, 5	IA
3. New certificate from a new manufacturer (replacement or addition)	1, 2, 3, 4, 5, 6, 9	1, 2, 3, 4, 5	IA_{IN}
4. Deletion of certificates (in case multiple certificates exist per material)	8	3	IA
5. New certificate for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free		1, 2, 3, 4, 5, 6	IB

b) European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/intermediate/or excipient

1. New certificate for an active substance from a new or an already approved manufacturer	3, 5, 9	1, 2, 3, 4, 5	IA_{IN}
2. New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	3, 6, 7	1, 2, 3, 4, 5	IA
3. Updated certificate from an already approved manufacturer	7	1, 2, 3, 4, 5	IA
4. Deletion of certificates (in case multiple certificates exist per material)	8	3	IA
5. New/updated certificate from an already-approved/new manufacturer using materials of human or animal origin for which an assessment of the risk with respect to potential contamination with adventitious agents is required			II

Conditions

1. The finished product release and end of shelf life specifications remain the same.
2. Unchanged (excluding tightening) additional (to the Pharmacopoeia of the Union) specifications for impurities (excluding residual solvents, provided they are in compliance with Union guidance) and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3. The manufacturing process of the active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of

viral safety data is required.

4. For active substance only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier.

5. The active substance/starting material/reagent/intermediate/excipient is not sterile.

6. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.

7. If gelatin manufactured from bones is to be used in a medicinal product for parenteral use, it should only be manufactured in compliance with the relevant country requirements.

8. At least one manufacturer for the same substance remains in the dossier.

9. If the active substance is a not a sterile substance but is to be used in a sterile medicinal product then according to the CEP it must not use water during the last steps of the synthesis or if it does the active substance must also be claimed to be free from bacterial endotoxins.

Documentation

1. Copy of the current (updated) Ph. Eur. Certificate of Suitability.

2. In case of an addition of a manufacturing site, the variation application form should clearly outline the 'present' and 'proposed' manufacturers as listed in section 2.5 of the application form.

3. Amendment of the relevant section(s) of the dossier.

4. Where applicable, a document providing information of any materials falling within the scope of the Pharmacopoeia of the Union monograph *on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* including those which are used in the manufacture of the active substance/excipient. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.

5. Where applicable, for active substance, a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the QP of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances — see the note under variation No B.II.b.1. The manufacture of intermediates also require a QP declaration, while as far as any updates to certificates for active substances and intermediates are concerned, a QP declaration is only required if, compared to the previously registered version of the certificate, there is a change to the actual listed manufacturing sites.

6. Suitable evidence to confirm compliance of the water used in the final steps of the synthesis of the active substance with the corresponding requirements on quality of water for pharmaceutical use.

B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Change of specification(s) of a former non-pharmacopoeial substance to fully comply with the Pharmacopoeia of the Union or with a pharmacopoeia of a Member State			
1. Active substance	1, 2, 3, 4, 5	1, 2, 3, 4	IA_{IN}
2. Excipient/active substance starting material	1, 2,4	1, 2, 3, 4	IA
b) Change to comply with an update of the relevant monograph of the Pharmacopoeia of the Union or pharmacopoeia of a Member State	1, 2, 4, 5	1, 2, 3, 4	IA
c) Change in specifications from a national pharmacopoeia of a Member State to the Pharmacopoeia of the Union.	1, 4, 5	1, 2, 3, 4	IA

Conditions

1. The change is made exclusively to fully comply with the pharmacopoeia. All the tests in the specification need to correspond to the pharmacopoeial standard after the change, except any additional supplementary tests.
2. Additional specifications to the pharmacopoeia for product specific properties are unchanged (e.g. particle size profiles, polymorphic form or, e.g. bioassays, aggregates).
3. No significant changes in qualitative and quantitative impurities profile unless the specifications are tightened
4. Additional validation of a new or changed pharmacopoeial method is not required
5. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.

Documentation

1. Amendment of the relevant section(s) of the dossier.
2. Comparative table of current and proposed specifications.
3. Batch analysis data (in a comparative tabulated format) on two production batches of the relevant substance for all tests in the new specification and additionally, where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch. For herbal medicinal products, comparative disintegration data may be acceptable.
4. Data to demonstrate the suitability of the monograph to control the substance, e.g. a comparison of the potential impurities with the transparency note of the monograph.

Note: there is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that reference is made to the 'current edition' in the dossier of an authorized medicinal product.

B.IV MEDICAL DEVICES

B.IV.1 Change of a measuring or administration device	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Addition or replacement of a device which is not an integrated part of the primary packaging			
1. Device authorized in the Union	1, 2, 3, 5, 6	1, 2, 4	IA_{IN}
2. Spacer device for metered dose inhalers or other device which may have a significant impact on the delivery of the active substance in the product (e.g. nebuliser)			II
b) Deletion of a device	4, 5	1, 5	IA_{IN}
c) Addition or replacement of a device which is an integrated part of the primary packaging			II

Conditions

1. The proposed measuring or administration device must accurately deliver the required dose for the product concerned in line with the approved posology and results of such studies should be available.
2. The new device is compatible with the medicinal product.
3. The change should not lead to substantial amendments of the product information.
4. The medicinal product can still be accurately delivered.
5. The medical device is not used as a solvent of the medicinal product.
6. If a measuring function is intended the dossier should cover the measuring function.

Documentation

1. Amendment of the relevant section(s) of the dossier, including description, detailed drawing and composition of the device material and supplier where appropriate, and including revised product information as appropriate.
2. Proof of Union marketing authorization of the device
3. Data to demonstrate accuracy, precision and compatibility of the device.
4. Samples of the new device where applicable.
5. Justification for the deletion of the device.

Note: for B.IV.1.c), applicants are reminded that any change which results in a 'new pharmaceutical form' requires the submission of an Extension application.

B.V. CHANGES TO A MARKETING AUTHORISATION APPLICATION DOSSIER RESULTING FROM OTHER REGULATORY PROCEDURES

B.V.a) *PMF/VAMF*

B.V.a.1 Inclusion of a new, updated or amended Plasma Master File in the marketing authorization dossier of a medicinal product. (PMF 2nd step procedure)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) First-time inclusion of a new Plasma Master File affecting the properties of the finished product			II
b) First-time inclusion of a new Plasma Master File not affecting the properties of the finished product		1, 2, 3, 4	IB
c) Inclusion of an updated/amended Plasma Master File when changes affect the properties of the finished product		1, 2, 3, 4	IB
d) Inclusion of an updated/amended Plasma Master File when changes do not affect the properties of the finished product	1	1, 2, 3, 4	IA_{IN}

Conditions

1. The updated or amended Plasma Master File has been granted a certificate of compliance with legislation of the Union in accordance with Appendix 1 to the Rules of authorization and assessment of medicinal products for human use subject to approval by the Commission.

Documentation

1. Declaration that the PMF Certificate and Evaluation Report are fully applicable for the authorized product, PMF holder has provided the PMF Certificate, Evaluation report and PMF dossier to the MAH (where the MAH is different to the PMF holder), the PMF Certificate and Evaluation Report replace the previous PMF documentation for this Marketing Authorization.
2. PMF Certificate and Evaluation Report.
3. An expert statement outlining all the changes introduced with the certified PMF and evaluating their potential impact on the finished products including product specific risk assessments.
4. The variation application form should clearly outline the ‘present’ and ‘proposed’ PMF Certificate (code number) in the MA dossier. When applicable, the variation application form should clearly list also all the other PMFs to which the medicinal product refers even if they are not the subject of the application.

B.V.a.2 Inclusion of a new, updated or amended Vaccine Antigen Master File in the marketing authorization dossier	Conditions to be fulfilled	Documentation to be supplied	Procedure type

of a medicinal product. (VAMF 2nd step procedure)			
a) First-time inclusion of a new Vaccine Antigen Master File			II
b) Inclusion of an updated/amended Vaccine Antigen Master File, when changes affect the properties of the finished product		1, 2, 3, 4	IB
c) Inclusion of an updated/amended Vaccine Antigen Master File, when changes do not affect the properties of the finished product	1	1, 2, 3, 4	IA_{IN}

Conditions

1. The updated or amended Vaccine Antigen Master File has been granted a certificate of compliance with legislation of the Union in accordance with Appendix 1 to the Rules of authorization and assessment of medicinal products for human within the Eurasian Economic Union.

Documentation

1. Declaration that the VAMF Certificate and Evaluation Report are fully applicable for the authorized product, VAMF holder has submitted the VAMF Certificate, Evaluation report and VAMF dossier to the MAH (where the MAH is different to the VAMF holder), the VAMF Certificate and Evaluation Report replace the previous VAMF documentation for this Marketing Authorization.
2. VAMF Certificate and Evaluation Report.
3. An expert statement outlining all the changes introduced with the certified VAMF and evaluating their potential impact on the finished products including product specific risk assessments.
4. The variation application form should clearly outline the 'present' and 'proposed' VAMF Certificate (code number) in the MA dossier. When applicable, the variation application form should clearly list also all the other VAMFs to which the medicinal product refers even if they are not the subject of the application.

B.V.b) ***Referral to the Expert Committee***

B.V.b.1 Update of the quality dossier intended to implement the outcome of a Union referral procedure	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The change implements the outcome of the referral	1	1, 2	IA_{IN}
b) The harmonization of the quality dossier was not part of the referral and the update is intended to harmonize it			II

Conditions 1. The outcome does not require further assessment.
Documentation 1. Attached to the cover letter of the variation application: A reference to the Expert Committee recommendation concerned. 2. The changes introduced during the referral procedure should be clearly highlighted in the submission.

C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES

C.I HUMAN MEDICINAL PRODUCTS

C.I.1 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The medicinal product is covered by the defined scope of the procedure	1	1, 2, 3	IA_{IN}
b) The medicinal product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure and no new additional data is required to be submitted by the MAH		1, 2, 3	IB
c) The medicinal product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure with new additional data submitted by the MAH		1, 3	II
Conditions 1. The variation implements the wording requested by the authority and it does not require the submission of additional information and/or further assessment.			
Documentation 1. Attached to the cover letter of the variation application: a reference to the Expert Committee recommendation concerned with the annexed Summary of Product Characteristics, Labelling or Package Leaflet. 2. A declaration that the proposed Summary of Product Characteristics, Labelling and Package Leaflet is identical for the concerned sections to that annexed to the Expert Committee recommendation. 3. Revised product information.			
C.I.2 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Implementation of change(s) for which no new		1, 2	IB

additional data is required to be submitted by the MAH			
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH (e.g. comparability)			II
Documentation 1. Attached to the cover letter of the variation application: national competent authority request, if applicable. 2. Revised product information.			
C.I.3 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Implementation of wording agreed by the competent authority	1	1, 2	IA_{IN}
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH		2	II
Conditions 1. The variation implements the wording requested by the competent authority and it does not require the submission of additional information and/or further assessment.			
Documentation 1. Attached to the cover letter of the variation application: reference to the agreement/assessment of the competent authority. 2. Revised product information.			
C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II
Note: this variation does not apply when the new data has been submitted under variation C.I.13. In such cases, the change(s) in the SmPC, labelling and/or package leaflet is covered by the scope of variation C.I.13.			
C.I.5 Change in the legal status of a medicinal product for centrally authorized products	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) For generic/hybrid/biosimilar medicinal products following an approved legal status change of the reference medicinal product		1, 2	IB
b) All other legal status changes			II
Documentation 1. Attached to the cover letter of the variation application: proof of authorization of the legal			

status change (e.g. reference to the competent authority of the Member State decision concerned).

2. Revised product information.

C.I.6 Change(s) to therapeutic indication(s)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Addition of a new therapeutic indication or modification of an approved one			II
b) Deletion of a therapeutic indication			IB

Note: where the change takes place in the context of the implementation of the outcome of a referral procedure, or — for a generic/hybrid/biosimilar product — when the same change has been done for the reference product, variations C.I.1 and C.I.2 apply, respectively.

C.I.7 Deletion of:	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) a pharmaceutical form		1, 2	IB
b) a strength		1, 2	IB

Documentation

1. Declaration that the remaining product presentation(s) are adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.
2. Revised product information

Note: in cases where a given pharmaceutical form or strength has received a marketing authorization which is separate to the marketing authorization for other pharmaceutical forms or strengths, the deletion of the former will not be a variation but the withdrawal of the marketing authorization.

C.I.8 Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use (*)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location		1, 2	IA_{IN}

Documentation

1. Summary of the pharmacovigilance system, or update of the relevant elements (as applicable):
   - — Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance and a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in the Rules of the Good Pharmacovigilance Practice of the Union.
   - — Contact details of the QPPV, Member States in which the QPPV resides and carries out his/her tasks
   - — PSMF location

2. PSMF number (if available)

Note: This variation covers the introduction of a PSMF irrespective of whether or not the technical dossier of the MA contained a DDPS.
Changes in QPPV, including contact details (telephone and fax numbers, postal address and e-mail address) and changes to the location of the PSMF (street, city, postcode, country) may be updated through the Common Register only (without the need for a variation).
Where the MAH makes use of the possibility to update the above information through the Common Register, the MAH must indicate in the marketing authorization that the updated information of those particulars is included in the database.

C.I.9 Change(s) to an existing pharmacovigilance system as described in the detailed description of the pharmacovigilance system (DDPS).	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Change in the QPPV and/or QPPV contact details and/or back-up procedure	1	1	IA_{IN}
b) Change(s) in the safety database and/or major contractual arrangements for the fulfilment of pharmacovigilance obligations, and/or change of the site undergoing pharmacovigilance activities	1, 2, 3	1	IA_{IN}
c) Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system (e.g. change of the major storage/archiving location, administrative changes)	1	1	IA
d) Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	4	1, 2	IA_{IN}

Conditions

1. The pharmacovigilance system itself remains unchanged.
2. The database system has been validated (when applicable).
3. Transfer of data from other database systems has been validated (when applicable).
4. The same changes to the DDPS are introduced for all medicinal products of the same MAH (same final DDPS version)

Documentation

1. Latest version of the DDPS and, where applicable, latest version of the product specific addendum. These should include for changes to the QPPV a) summary CV of the new QPPV, b) proof of QPPV EudraVigilance registration, and c) a new statement of the MAH and the QPPV regarding their availability and the means for notification of adverse reactions signed by the new QPPV and the MAH, and reflecting any other consequential changes, e.g. to the organisation chart.
   When the QPPV and/or QPPV contact details are not included in a DDPS or no DDPS exists, the submission of a revised DDPS version is not required and the application form is to be provided.
2. Reference of the application/procedure and product in which the change(s) were accepted.

Note: C.I.9 covers changes to an existing pharmacovigilance system 1) for veterinary medicinal products and 2) for human medicinal products that have not yet introduced a PSMF.

Note for a): Changes in QPPV, including contact details (telephone and fax numbers, postal address and e-mail address) may be updated through the Common Register only (without the need for a variation). Where the MAH makes use of the possibility to update this information through the Common Register, the MAH must indicate in the marketing authorization that the updated information of those particulars is included in the database.

Note for d): The assessment of a DDPS submitted as part of a new MAA/Extension/Variation may give rise to changes at the request of the national competent authority/EMA in this DDPS. Where this occurs, the same change(s) can be introduced to the DDPS in other marketing authorizations of the same MAH by submitting a (grouped) Type IA_{IN} variation.

C.I.10 Change in the frequency and/or date of submission of periodic safety update reports (PSUR) for human medicinal products	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1, 2	IA_{IN}

Conditions

1. The change in the frequency and/or date of submission of the PSUR has been agreed by the national competent authority.

Documentation

1. Attached to the cover letter of the variation application: A reference to the agreement of the competent authority.
2. Revised frequency and/or date of submission of the PSUR.

Note: this variation applies only when the PSUR cycle is specified in the marketing authorization by other means than a reference to the list of Union reference dates and where PSUR submission is required.

C.I.11 Introduction of, or change(s) to, the obligations and conditions of a marketing authorization, including the risk management plan	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Implementation of wording agreed by the competent authority	1	1, 2	IA_{IN}
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the competent authority is required (13)			II

Conditions

1. The variation implements the action requested by the authority and it does not require the submission of additional information and/or further assessment.

Documentation

1. Attached to the cover letter of the variation application: A reference to the relevant decision of the competent authority.

2. Update of the relevant section of the dossier.

Note: this variation covers the situation where the only change introduced concerns the conditions and/or obligations of the marketing authorization, including the risk management plan and the conditions and/or obligations of marketing authorizations under exceptional circumstances and conditional marketing authorization.

C.I.12 Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1, 2	IA_{IN}

Conditions

1. The medicinal product is included or removed from the list of medicinal products that are subject to additional monitoring (as applicable)

Documentation

1. Attached to the cover letter of the variation application: A reference to the list of medicinal products that are subject to additional monitoring
2. Revised product information

Note: this variation covers the situation where the inclusion or deletion of the black symbol and explanatory statements is not done as part of another regulatory procedure (e.g. renewal or variation procedure affecting the product information).

C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority (*)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II

Note: in cases where the assessment by the competent authority of the data submitted leads to a change of the Summary of Product Characteristics, Labelling or Package Leaflet, the relevant amendment to the Summary of Product Characteristics, Labelling or Package Leaflet is covered by the variation.

* This variation does not apply to variations that can be considered as Type IB by default under any other section of this Annex.

D. PMF/VAMF

D.1 Change in the name and/or address of the VAMF certificate holder	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA_{IN}

Conditions

1. The VAMF certificate holder must remain the same legal entity.

Documentation

1. A formal document from a relevant official body (e.g. Tax Service) in which the new name or new address is mentioned.

D.2 Change in the name and/or address of the PMF certificate holder	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA_{IN}

Conditions

1. The PMF certificate holder must remain the same legal entity.

Documentation

1. A formal document from a relevant official body (e.g. Tax Service) in which the new name or new address is mentioned.

D.3 Change or transfer of the current PMF certificate holder to a new PMF certificate holder, i.e. different legal entity	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2, 3, 4, 5, 6	IA_{IN}

Documentation

1. A document including the identification (name and address) of the current PMF Holder (transferor) and the identification (name and address) of the person to whom the transfer is to be granted (transferee) together with the proposed implementation date — signed by both companies.
2. Copy of the latest PMF Certificate page 'Plasma Master File (PMF) Certificate of compliance with Union legislation'.
3. Proof of establishment of the new holder (Excerpt of the commercial register and the Russian translation of it) — signed by both companies.
4. Confirmation of the transfer of the complete PMF documentation since the initial PMF certification to the transferee — signed by both companies.
5. Letter of Authorization including contact details of the person responsible for communication between the competent authority and the PMF holder — signed by the transferee.
6. Letter of Undertaking to fulfil all open and remaining commitments (if any) — signed by the transferee.

D.4 Change in the name and/or address of a blood establishment including blood/plasma collection centers	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1, 2	1, 2, 3	IA

Conditions

1. The blood establishment must remain the same legal entity.
2. The change must be administrative (e.g. merger, take over); change in the name of the blood establishment/collection center provided the blood establishment must remain the same.

Documentation

1. Signed declaration that the change does not involve a change of the quality system within the blood establishment.
2. Signed declaration that there is no change in the list of the collection centers.
3. Updated relevant sections and annexes of the PMF dossier.

D.5 Replacement or addition of a blood/plasma collection center within a blood establishment already included in the PMF	Conditions to be fulfilled	Documentation to be supplied	Procedure type

		1, 2, 3	IB
Documentation 1. Epidemiological data for viral markers related to the blood/plasma collection center covering the last 3 years. For newly opened center(s) or in case no data are yet available, a declaration that epidemiological data will be provided at the time of the next annual update(s). 2. Statement that the center is working under the same conditions as the other centers belonging to the blood establishment, as specified in the standard contract between blood establishment and PMF holder. 3. Updated relevant sections and annexes of the PMF dossier.			
D.6 Deletion or change of status (operational/non-operational) of establishment(s)/center(s) used for blood/plasma collection or in the testing of donations and plasma pools	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1, 2	1	IA
Conditions 1. The reason for deletion or change of status should not be related to a GMP issue. 2. The establishments(s)/center(s) should comply with the legislation in terms of inspections in case of change of status from non-operational to operational.			
Documentation 1. Updated relevant sections and annexes of the PMF dossier.			
D.7 Addition of a new blood establishment for the collection of blood/plasma not included in the PMF	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II
D.8 Replacement or addition of a blood center for testing of donations and/or plasma pools within an establishment already included in the PMF	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2	IB
Documentation 1. Statement that the testing is performed following the same SOPs and/or test methods as already accepted. 2. Updated relevant sections and annexes of the PMF dossier.			
D.9 Addition of a new blood establishment for testing of donations and/or plasma pool not included in the PMF	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II
D.10 Replacement or addition of a new blood establishment or center(s) in which storage of plasma is carried out	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2	IB
Documentation 1. Statement that the storage center is working following the same SOPs as the already			

accepted establishment. 2. Updated relevant sections and annexes of the PMF dossier.			
D.11 Deletion of a blood establishment or center(s) in which storage of plasma is carried out	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA
Conditions 1. The reason for deletion should not be related to a GMP issues.			
Documentation 1. Updated relevant sections and annexes of the PMF dossier.			
D.12 Replacement or addition of an organization involved in the transport of plasma.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1	IB
Documentation 1. Updated relevant sections and annexes of the PMF dossier, including a list of all the blood establishments using this transport organization, a summary of the system in place to ensure that the transport is performed under appropriate conditions (time, temperature and GMP compliance) and confirmation that transport conditions are validated.			
D.13 Deletion of an organization involved in the transport of plasma	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA
Conditions 1. The reason for deletion should not be related to GMP issues.			
Documentation 1. Updated relevant sections and annexes of the PMF dossier.			
D.14 Addition of a test kit authorized for marketing in the Union to test individual donations as a new test kit or as a replacement of an existing test kit	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1, 2	IA
Conditions 1. The new test kit is authorized for marketing in the Union as a device.			
Documentation 1. List of testing site(s) where the kit is used. 2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing as requested in the ‘Guideline on the scientific data requirements for a PMF’.			
D.15 Addition of a test kit not authorized for marketing in the Union to test individual donations as a new test kit or as a replacement of an existing test kit	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The new test kit has not previously been			II

approved in the PMF for any blood center for testing of donations			
b) The new test kit has been approved in the PMF for other blood center(s) for testing of donations		1, 2	IA
Documentation 1. List of testing center(s) where the kit is currently used and a list of testing center(s) where the kit will be used. 2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing as requested in the Union guidance on the scientific data requirements for a PMF.			
D.16 Change of kit/method used to test pools (antibody or antigen or NAT test).	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II
D.17 Introduction or extension of inventory hold procedure.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA
Conditions 1. The inventory hold procedure is a more stringent procedure (e.g. release only after retesting of donors).			
Documentation 1. Updated relevant sections of the PMF dossier, including the rationale for introduction or extension of inventory hold period, the sites where the inventory hold takes place and for changes to procedure, a decision tree including new conditions.			
D.18 Removal of inventory hold period or reduction in its length.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1	IB
Documentation 1. Updated relevant sections of the PMF dossier			
D.19 Replacement or addition of blood containers (e.g. bags, bottles)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The new blood containers are authorized for marketing in the Union as a device	1, 2	1	IA
b) The new blood containers are not authorized for marketing in the Union as a device			II
Conditions 1. The container is authorized for marketing in the Union as a device. 2. The quality criteria of the blood in the container remain unchanged.			
Documentation 1. Updated relevant sections and annexes of the PMF dossier, including the name of container, manufacturer, anticoagulant solution specification, confirmation of authorization for			

marketing in the Union and the name of the blood establishments where the container is used.			
D.20 Change in storage/transport	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) storage and/or transport conditions	1	1	IA
b) maximum storage time for the plasma	1, 2	1	IA
Conditions 1. The change should tighten the conditions and be in compliance with Pharmacopoeia of the Union requirements for Human Plasma for Fractionation. 2. The maximum storage time is shorter than previously.			
Documentation 1. Updated relevant sections and annexes of the PMF dossier, including detailed description of the new conditions, confirmation of validation of storage/transport conditions and the name of the blood establishment(s) where the change takes place (if relevant).			
D.21 Introduction of test for viral markers when this introduction will have significant impact on the viral risk assessment.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II
D.22 Change in the plasma pool preparation (e.g. manufacturing method, pool size, storage of plasma pool samples)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1	IB
Documentation 1. Updated relevant sections of the PMF dossier.			
D.23 Change in the steps that would be taken if it is found retrospectively that donation(s) should have been excluded from processing (‘look-back’ procedure).	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II

APPENDIX 20
to the Rules of authorization
and assessment of medicinal products
for human use

RULES

of assessment of variations to a marketing authorizations application dossier for medicinal products for human use

I. GENERAL PROVISIONS

1.1. These Rules apply to the variations of marketing authorizations for medicinal products for human use as referred to in paragraphs 1.1.3 to 1.1.5 of Appendix 19 to the Rules of authorization and assessment of medicinal products for human use subject to approval Eurasian Economic Commission (hereinafter referred to as the Rules of authorization of medicinal products); they provide details on the application of the relevant procedures and shall be read in conjunction with Appendix 19 to the Rules of authorization of medicinal products.

1.2. Definitions relevant to this Appendix are provided in Eurasian Economic Union (hereinafter referred to as the Union) documents governing medicinal products in the Union.

1.3. Reference in this Appendix to 'Member States concerned', in accordance with paragraph 1.2.6 of Appendix 19 to the Rules of authorization of medicinal products, is to be understood as each Member State of the Union (hereinafter referred to as Member State) whose competent authority has granted a marketing authorization for the medicinal product in question. Reference to 'concerned Member States' is to be understood as all Member States concerned.

II. PROCEDURAL GUIDANCE ON THE HANDLING OF VARIATIONS

A marketing authorization lays down the terms under which the marketing of a medicinal product is authorized in the Union. A marketing authorization is composed of:

a decision granting the marketing authorization issued by the competent authority of the Member State; and

documents and data submitted by the applicant in accordance with Appendix 1 the Rules of authorization of medicinal products to the competent authority (assessment organization) of the Member State.

Appendix 19 to the Rules of authorization of medicinal products governs the procedures for the amendment of the decision granting the marketing authorization and of the technical dossier.

These Rules cover the following categories of variations, defined in paragraph 1.3 of Appendix 19 to the Rules of authorization of medicinal products:

Minor variations of Type IA

Minor variations of Type IB

Major variations of Type II

Extensions

Urgent safety restriction

The competent authority (assessment organization) of the reference Member State is available to address any questions which holders may have regarding a particular upcoming variation. Where appropriate, a pre-submission discussion may be organized with competent authority (assessment organization) of the reference Member State in order to obtain further

regulatory and procedural advice from the competent authority (assessment organization) of the reference Member State.

Any information related to the implementation of a given variation should be immediately provided by the holder upon the request of the relevant authority.

2.1. Minor variations of Type IA

Hereby guidance is provided on the application of paragraphs 1.7, 2.1, 2.4, 3.1, 3.4, 3.5, 4.2.1, and 4.2.2 of Appendix 19 to the Rules of authorization of medicinal products to minor variations of Type IA. Such minor variations do not require any prior approval (however, the application shall be submitted before the implementation of the variation in the case of variations entailing amendments to product information as provided in paragraph 1.6 of Appendix 19 to the Rules of authorization of medicinal products), but must be notified by the holder within 365 calendar days (12 months) following implementation (‘Do and Tell’ procedure). However, certain minor variations of Type IA require immediate notification after implementation, in order to ensure the continuous supervision of the medicinal product.

The Annex V to Appendix 19 to the Rules of authorization of medicinal products clarifies the conditions which must be met in order for a change to follow a Type IA notification procedure, and specifies which minor variations of Type IA must be notified immediately following implementation.

2.1.1. Submission of Type IA notifications

Minor variations of Type IA do not require prior examination by the authorities before they can be implemented by the holder. However, the application shall be submitted before the implementation of the variation in the case of variations entailing amendments to product information as provided in paragraph 1.6 of Appendix 19 to the Rules of authorization of medicinal products.

However, at the latest within 365 calendar days (12 months) from the date of the implementation, the applicant must submit simultaneously to the competent authority (assessment organization) of the reference Member State an application (notification) containing the elements listed in Annex IV of Appendix 19 to the Rules of authorization of medicinal products.

The application shall be submitted before the implementation of the variation in the case of variations entailing amendments to product information as provided in paragraph 1.6 of Appendix 19 to the Rules of authorization of medicinal products.

It is possible for an applicant to include a minor variation of Type IA which is not subject to immediate notification in the submission of a minor variation of Type IA for immediate notification or with any other variation.

The conditions laid down in paragraphs 1.7.2 and 3.4.2 of Appendix 19 to the Rules of authorization of medicinal products should be fulfilled.

The applicant may group several minor variations of Type IA under a single notification, as established in 1.7.2 and 3.4.2 of Appendix 19 to the Rules of authorization of medicinal products. Specifically, two possibilities exist for the grouping of variations of Type IA:

a) The applicant may group several minor variations of Type IA regarding the terms of one single marketing authorization provided that they are notified at the same time to the same relevant authority.

b) The applicant may group one or more minor variations of Type IA to the terms of several marketing authorizations under a single notification provided that the variations are the same for all marketing authorizations concerned and they are notified at the same time to the same competent authority (assessment organization).

The 365 calendar days (12 months) deadline to notify minor variations of Type IA allows holders to collect Type IA variations for their medicinal products during a year. However, the notification of these variations in a single submission is only possible where the conditions for grouping apply (same variations for all medicinal products concerned).

Therefore, it may be the case that the submission of variations implemented over a period of 365 calendar days (12 months) (so called ‘annual report’) requires several submissions; e.g. one referring to a single minor variation of Type IA, another referring to group of minor variations of Type IA to the terms of one marketing authorization, and another referring to group of the minor variations of Type IA to the terms of several marketing authorizations.

The notification must contain the elements listed in Annex IV to Appendix 19 to the Rules of authorization of medicinal products, presented as follows in accordance with the appropriate headings and numbering of Common Technical Document format:

Cover letter;

The completed variation application form, including the details of the marketing authorization(s) concerned, as well as a description of all variations submitted together with their date of implementation as applicable. Where a variation is the consequence of, or related to, another variation, a description of the relation between these variations should be provided in the appropriate section of the application form;

Reference to the variation code as laid down in the Annex V to Appendix 19 to the Rules of authorization of medicinal products, indicating that all conditions and documentation requirements are met or, where applicable, reference to a classification recommendation published in accordance with paragraph 1.5 of Appendix 19 to the Rules of authorization of medicinal products used for the relevant application;

All documentation specified in Annex V to Appendix 19 to the Rules of authorization of medicinal products;

In case that the variations affect the summary of product characteristics, labelling or package leaflet: the revised product information (the summary of product characteristics, labelling or package leaflet), normative document presented in the appropriate format, as well as the relevant translations into official languages as required by legislation of the Member States. Where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the minor variation of Type IA, mock-ups of the inner packaging and of the outer packaging should be provided to the competent authority (assessment organization).

For variations referred to in paragraph 1.1.3 of Appendix 19 to the Rules of authorization of medicinal products, the competent authority (assessment organization) of the reference Member State should additionally receive the list of dispatch dates indicating the appropriate variation applications the dates on which the applications have been sent to each Member State concerned and confirmation that the fees for variation to the terms of the marketing authorization (and the assessment thereof) have been paid as required by the Member State concerned legislation.

For variations referred to in paragraph 1.1.4 of Appendix 19 to the Rules of authorization of medicinal products, confirmation that the fees for variation to the terms of the marketing authorization (and the assessment thereof) have been paid as required by the Member States legislation.

For grouped minor variations of Type IA concerning several marketing authorizations from the same holder in accordance with paragraph 1.7 or 3.4 of Appendix 19 to the Rules of authorization of medicinal products, a common cover letter and application form should be submitted together with separate supportive documentation and revised product information (if applicable) for each medicinal product concerned. This will allow the relevant authorities to update the dossier of each marketing authorization included in the group with the relevant amended or new information.

2.1.2. Type IA variations referred to in paragraph 1.1.3 of Appendix 19 to the Rules of authorization of medicinal products

Where a minor variation of type IA is made, the applicant shall submit simultaneously to all relevant authorities (assessment organizations) an application in paper and/or electronic format as laid down in Appendix 2 to the Rules of authorization of medicinal products and confirmation that the relevant fees have been paid as required by the Member States legislation.

The applicant shall submit to the competent authority (assessment organization) of the reference Member State a variation application (notification) containing the elements listed in Annex IV of Appendix 19 to the Rules of authorization of medicinal products.

The competent authority (assessment organization) of the reference Member State within 5 business days beginning with the day the variation application is submitted, having checked of completeness and accuracy of the format of the documents submitted, shall ensure the access of relevant authorities of Member States concerned to the variation application (notification) via Integrated System.

The competent authority (assessment organization) of the reference Member State will review the Type IA notification within 30 calendar days following receipt thereof.

By Day 30, the competent authority (assessment organization) of the reference Member State will inform the applicant and competent authority (assessment organization) Member States concerned of the outcome of its review.

Any amendment to the decision granting the marketing authorization in accordance with Appendix 19 to the Rules of authorization of medicinal products shall be implemented within 180 calendar days following the receipt of the information referred to in paragraph 2.4.1(4) or 3.5.1(2) of Appendix 19 to the Rules of authorization of medicinal products, provided that the documents necessary for the amendment of the marketing authorization have been submitted to competent authorities (assessment organizations) the Member States concerned.

In the case of variations entailing amendments to product information as provided in paragraph 1.6 of Appendix 19 to the Rules of authorization of medicinal products, relevant competent authorities within 10 business days beginning with the day the decision is made on the variation, shall make publicly available the information on variations made in the Common Register of authorized medicinal products (hereinafter referred to as the Common Register) together with the approved summary of product characteristics, medication guide, mock-ups of the packaging, normative document in accordance with the Procedure for establishing and maintaining the Common Register and shall issue the updated summary of product characteristics, medication guide, mock-ups of the packaging, normative document, certificate of the marketing authorization to the applicant, where necessary.

The relevant competent authorities (assessment organizations) may extend that period to 90 calendar days where the applicant has submitted multiple groupings of variations in accordance with paragraphs 1.7.2 and 1.7.3 of this Appendix 19 to the Rules of authorization of medicinal products.

Where one or several minor variations of Type IA are submitted as part of one notification, the reference Member State will inform the holder which variation(s) have been accepted or rejected following its review. The marketing authorization holder must not implement the rejected variation(s).

While in the case of minor variations of Type IA, failure to provide all necessary documentation in the application will not necessarily lead to the immediate rejection of the variation if the holder provides any missing documentation Appendix 19 to the Rules of authorization of medicinal products immediately upon the request of the relevant authority, it should be highlighted that a minor variation of Type IA may in specific circumstances be rejected with the consequence that the holder must immediately cease to apply already implemented variations concerned.

2.1.3. Type IA variations referred to in paragraph 1.1.4 of Appendix 19 to the Rules of authorization of medicinal products

Where a minor variation of type IA is made, the applicant shall submit simultaneously to the competent authority (assessment organization) an application in paper and/or electronic format as laid down in Appendix 2 to the Rules of authorization of medicinal products and confirmation that the relevant fees have been paid as required by the Member States legislation.

The applicant shall submit to the competent authority (assessment organization) of the reference Member State a variation application (notification) containing the elements listed in Annex IV of Appendix 19 to the Rules of authorization of medicinal products. The competent

authority (assessment organization) will review the Type IA notification within 30 calendar days following receipt.

By Day 30, the competent authority (assessment organization) will inform the applicant of the outcome of its review.

Any amendment to the decision granting the marketing authorization in accordance with Appendix 19 to the Rules of authorization of medicinal products shall be implemented within 180 calendar days following the date of information to the applicant of the outcome of the review, provided that the documents necessary for the amendment of the marketing authorization have been submitted to the competent authority (assessment organization).

In the case of variations entailing amendments to product information as provided in paragraph 1.6 of Appendix 19 to the Rules of authorization of medicinal products, relevant competent authorities within 10 business days beginning with the day the decision is made on the variation, shall make publicly available the information on variations made in the Common Register of authorized medicinal products (hereinafter referred to as the Common Register) together with the approved summary of product characteristics, medication guide, mock-ups of the packaging, normative document in accordance with the Procedure for establishing and maintaining the Common Register and shall issue the updated summary of product characteristics, medication guide, mock-ups of the packaging, normative document, certificate of the marketing authorization to the applicant, where necessary.

The competent authority (assessment organization) may extend the periods referred to in subparagraphs 2 or 4 of this paragraph to 90 calendar days where the applicant has submitted multiple groupings of variations in accordance with paragraphs 1.7.2 and 1.7.3 of this Appendix.

Where one or several minor variations of Type IA are submitted as part of one notification, the competent authority (assessment organization) will inform the applicant which variation(s) have been accepted or rejected following its review.

While in the case of minor variations of Type IA, failure to provide all necessary documentation in the application will not necessarily lead to the immediate rejection of the variation if the applicant provides any missing documentation immediately on request of the relevant authority, it should be highlighted that a minor variation of Type IA may in specific circumstances be rejected with the consequence that the holder must immediately cease to apply already implemented variations concerned.

2.2. Minor variations of Type IB

Hereby guidance is provided on the application of paragraphs 1.7, 2.2, 2.4, 3.2, 3.5, 4.2.1, and 4.2.2 of Appendix 19 to the Rules of authorization of medicinal products to minor variations of Type IB.

Appendix 19 to the Rules of authorization of medicinal products set out a list of changes to be considered as minor variations of Type IB. Such minor variations must be notified before implementation or approved by the competent authority in the case of variations entailing amendments to product information as provided in paragraph 1.6 of Appendix 19 to the Rules of authorization of medicinal products the application for which shall be submitted before the implementation of the variation.

The holder must wait a period of 30 calendar days to ensure that the notification is deemed acceptable by the competent authority (assessment organization) before implementing the change if within that period, the competent authority (assessment organization) has not sent the applicant a refuse to amend the terms of the marketing authorization (‘Tell, Wait and Do’ procedure).

2.2.1. Submission of Type IB notifications

Applicants may group under a single notification the submission of several minor variations of Type IB regarding the same marketing authorization, or group the submission of one or more minor variation(s) of Type IB with other minor variations regarding the same marketing authorization, provided that this corresponds to one of the cases listed in Annex III of Appendix 19 to the Rules of authorization of medicinal products, or when this has been agreed

previously with the competent authority (assessment organization) of the reference Member State.

In addition, for medicinal products authorized in one Member State, the applicant may also group several minor variations of Type IB affecting several marketing authorizations in a single Member State, or one or more minor variation(s) of Type IB with other minor variations affecting several marketing authorizations in a single Member State provided that:

the variations are the same for all the marketing authorizations concerned,

the variations are submitted at the same time to the competent authority (assessment organization), and

the competent authority (assessment organization) has previously agreed to the grouping.

Furthermore, where the same minor variation of Type IB or the same group of minor variations (as explained above) affect several marketing authorizations owned by the same holder, the holder may submit these variations as one application for 'work-sharing'.

The applicant shall submit to the competent authority (assessment organization) reference Member State the application (notification) containing the elements listed in Annex IV to Appendix 19 to the Rules of authorization of medicinal products, presented as follows in accordance with the appropriate headings and numbering of the CTD format:

Cover letter.

The completed variation application form, including the details of the marketing authorizations(s) concerned. Where a variation is the consequence of or related to another variation, a description of the relation between these variations should be provided in the appropriate section of the application form. Where a variation is considered unclassified, a detailed justification for its submission as a Type IB notification must be included.

Reference to the variation code as laid down in the Annex V to Appendix 19 to the Rules of authorization of medicinal products, indicating that all conditions and documentation requirements are met or, where applicable, reference to a classification recommendation published in accordance with paragraph 1.5 of Appendix 19 to the Rules of authorization of medicinal products used for the relevant application.

Relevant documentation in support of the proposed variation including any documentation specified in the Annex V to Appendix 19 to the Rules of authorization of medicinal products.

For variations requested by the competent authority resulting from new data submitted, e.g. pursuant to post authorization conditions or in the framework of pharmacovigilance obligations, a copy of the competent authority (assessment organization) request should be annexed to the cover letter.

In case that the variations affect the summary of product characteristics, labelling, package leaflet or normative document: the revised product information (the summary of product characteristics, labelling, package leaflet) or normative document presented in the appropriate format, as well as the relevant translations into official languages of the Member States as required. Where the overall design and readability of the outer and/or immediate packaging is affected by the minor variation of Type IB, mock-ups should be provided to the competent authority (assessment organization).

For variations referred to in paragraph 1.1.3 of Appendix 19 to the Rules of authorization of medicinal products, the competent authority (assessment organization) of the reference Member State should additionally receive the list of dispatch dates indicating the appropriate type IB variation applications the dates on which the applications have been sent to each Member State concerned and confirmation that the fees for variation to the terms of the marketing authorization (and the assessment thereof) have been paid as required by the Member State concerned legislation.

For variations referred to in paragraph 1.1.4 of Appendix 19 to the Rules of authorization of medicinal products, confirmation that the fees for variation to the terms of the marketing authorization (and the assessment thereof) have been paid as required by the Member States legislation.

2.2.2. Review of type IB variations referred to in paragraph 1.1.3 of Appendix 19 to the Rules of authorization of medicinal products

Where a minor variation of type IB is made, the applicant shall submit simultaneously to all relevant authorities (assessment organizations) an application in paper and/or electronic format as laid down in Appendix 2 to the Rules of authorization of medicinal products and confirmation that the relevant fees have been paid as required by the Member States legislation.

The applicant shall submit to the competent authority (assessment organization) of the reference Member State a variation application (notification) containing the elements listed in Annex IV of Appendix 19 to the Rules of authorization of medicinal products.

The competent authority (assessment organization) of the reference Member State within 5 business days beginning with the day the variation application is submitted to the reference Member State, having checked of completeness and accuracy of the format of the documents submitted including whether the proposed change can be considered a minor variation of Type IB, shall ensure the access of relevant authorities of Member States concerned to the variation application (notification) via Integrated System.

When the proposed variation is not considered a minor variation of Type IB following the Annex V to Appendix 19 to the Rules of authorization of medicinal products or has not been classified as a minor variation of Type IB in a recommendation pursuant to 1.5 of Appendix 19 to the Rules of authorization of medicinal products, and the competent authority (assessment organization) of the reference Member State is of the opinion that it may have a significant impact on the quality, safety or efficacy of the medicinal product, the reference Member State will inform the Member States concerned and the applicant immediately.

If the concerned Member States do not disagree within further 10 calendar days, the applicant will be requested to revise its application and to complete it in accordance with the requirements for a major variation of Type II application. Following receipt of the valid revised variation application, a Type II assessment procedure will be initiated.

If the concerned Member States disagree with the competent authority (assessment organization) of the reference Member State, the competent authority (assessment organization) of the reference Member State must take the final decision on the classification of the proposed variation having taken into account the concerned Member States comments received.

When the competent authority (assessment organization) of the reference Member State is of the opinion that the proposed variation can be considered a minor variation of Type IB, the applicant will be informed of the outcome of the validation.

Within 30 calendar days following the acknowledgement of receipt of a valid notification, the competent authority (assessment organization) of the reference Member State will notify the applicant of the outcome of the procedure. If the competent authority (assessment organization) of the reference Member State has not sent the applicant its opinion on the notification within 30 calendar days following the acknowledgement of receipt of a valid notification, the notification will be deemed acceptable.

In case of an unfavorable outcome, the applicant may reapply the application (notification) to the competent authority (assessment organization) of the reference Member State within 30 days to take due account of the grounds for the non-acceptance of the variation.

If the applicant does not amend the notification as requested by the competent authority (assessment organization), the variation will be deemed rejected by all relevant authorities.

Within 30 calendar days of receipt of the amended notification, the competent authority (assessment organization) of the reference Member State shall consider submitted documents and particulars and will inform the applicant of its final acceptance or rejection of the variation(s) (including the grounds for the unfavorable outcome). Concerned Member States will be informed accordingly.

Where a group of minor variations were submitted as part of one notification, the competent authority (assessment organization) of the reference Member Stat will inform the applicant and the concerned Member States which variation(s) have been accepted or rejected following its review.

Where necessary, the relevant authorities will update the marketing authorization within 180 calendar days following closure of the procedure by the competent authority (assessment organization) of the reference Member State, provided that the documents necessary for the amendment of the marketing authorization have been submitted to the Member States concerned. However, the accepted minor variations of Type IB variation may be implemented without awaiting the update of the marketing authorization, except of variations entailing amendments to product information as provided in paragraph 1.6 of Appendix 19 to the Rules of authorization of medicinal products.

In the case within 10 business days beginning with the day the decision is made on the variation, relevant competent authorities shall make publicly available the information on variations made in the Common Register of authorized medicinal products (hereinafter referred to as the Common Register) together with the approved summary of product characteristics, medication guide, mock-ups of the packaging, normative document in accordance with the Procedure for establishing and maintaining the Common Register and shall issue the updated summary of product characteristics, medication guide, mock-ups of the packaging, normative document, certificate of the marketing authorization to the applicant, where necessary.

The relevant competent authorities (assessment organizations) may extend the period for assessment and document issuance to 90 calendar days where the applicant has submitted multiple groupings of variations in accordance with paragraphs 1.7.2 and 1.7.3 of this Appendix 19 to the Rules of authorization of medicinal products.

2.2.3. Review of type IB variations referred to in paragraph 1.1.4 of Appendix 19 to the Rules of authorization of medicinal products

Where a minor variation of type IB is made, the applicant shall submit simultaneously to all competent authority (assessment organization) an application in paper and/or electronic format as laid down in Appendix 2 to the Rules of authorization of medicinal products and confirmation that the relevant fees have been paid as required by the Member States legislation.

The applicant shall submit to the competent authority (assessment organization) of the reference Member State a variation application (notification) containing the elements listed in Annex IV of Appendix 19 to the Rules of authorization of medicinal products.

The competent authority (assessment organization) of the reference Member State within 5 business days will check completeness and accuracy of the format of the documents submitted incleding whether the proposed change can be considered a minor variation of Type IB, and whether the notification is correct and complete (‘validation’).

When the notification meets the requirements as set out in paragraph 3.2.1 of Appendix 19 to the Rules of authorization of medicinal products, competent authority (assessment organization) of the reference Member State within 30 calendar days shall confirm the receipt of a valid notification.

When the proposed variation is not considered a minor variation of Type IB following the Annex V of Appendix 19 to the Rules of authorization of medicinal products or has not been classified as a minor variation of Type IB in a recommendation pursuant to paragraph 1.5 of the Rules of authorization of medicinal products, and the competent authority (assessment organization) is of the opinion that it may have a significant impact on the quality, safety or efficacy of the medicinal product, the applicant will be requested to revise its application and to complete it in accordance with the requirements for a major variation of Type II application. Following receipt of the valid revised variation application, a Type II assessment procedure will be initiated.

Within 30 calendar days following the acknowledgement of receipt of a valid notification, the competent authority (assessment organization) will notify the applicant of the outcome of the procedure. If the competent authority (assessment organization) has not sent the applicant its opinion on the notification in writing or electronically within 30 calendar days following the acknowledgement of receipt of a valid notification, the notification will be deemed acceptable by the competent authority (assessment organization).

When the competent authority (assessment organization) of the reference Member State is of the opinion that the applicant's variation notification will not be deemed acceptable, the competent authority (assessment organization) of the reference Member State shall notify the applicant of that opinion and the reasons thereof.

In case of an unfavorable outcome, the applicant may reapply the application (notification) to the competent authority (assessment organization) of the reference Member State within 30 days to take due account of the grounds for the non-acceptance of the variation.

If the applicant does not apply the amended notification in accordance with the Rules of authorization of medicinal products, the variation will be deemed rejected.

Within 30 days of receipt of the amended notification, the competent authority (assessment organization) will inform the applicant of its final acceptance or rejection of the variation(s) (including the grounds for the unfavorable outcome).

Where a group of minor variations were submitted as part of one notification, the national competent authority will inform the holder which variation(s) have been accepted or rejected following its review.

Where necessary, the national competent authority will update the marketing authorization within 180 calendar days following closure of the procedure, provided that the documents necessary for the amendment of the marketing authorization have been submitted to the national competent authority. However, the accepted minor variations of Type IB may be implemented without awaiting the update of the marketing authorization.

In the case of variations entailing amendments to product information as provided in paragraph 1.6 of Appendix 19 to the Rules of authorization of medicinal products, the competent authority of the reference Member State within 10 business days beginning with the day the decision is made on the variation, shall make publicly available the information on variations made in the Common Register together with the approved summary of product characteristics, medication guide, mock-ups of the packaging, normative document in accordance with the Procedure for establishing and maintaining the Common Register and shall issue the updated summary of product characteristics, medication guide, mock-ups of the packaging, normative document, certificate of the marketing authorization to the applicant, where necessary.

The relevant competent authorities (assessment organizations) may extend the period for assessment and document issuance to 90 calendar days where the applicant has submitted multiple groupings of variations in accordance with paragraphs 1.7.2 and 1.7.3 of this Appendix 19 to the Rules of authorization of medicinal products.

2.3. Major variations of Type II

Hereby guidance is provided on the application of paragraphs 1.7, 2.3, 2.4, 2.6, 3.3 to 3.5, 4.2.1 and 4.2.2 of Appendix 19 to the Rules of authorization of medicinal products to minor variations of Type II.

The Variations Regulation and the Annex to these guidelines set out a list of changes to be considered as major variations of Type II. Such major variations require approval of the relevant competent authority before implementation.

2.3.1. Submission of Type II applications

The applicant shall submit to the competent authority (assessment organization) of the reference Member State an application in paper and/or electronic format as laid down in Appendix 2 to the Rules of authorization of medicinal products and confirmation that the relevant fees have been paid as required by the reference Member State legislation, as well as the dossier containing the elements listed in Annex IV to Appendix 19 to the Rules of authorization of medicinal products

Applicants may group under a single notification the submission of several major variations of Type II regarding the same marketing authorization, or group the submission of one or more major variation(s) of Type II with other minor variations regarding the same marketing authorization, provided that this corresponds to one of the cases listed in Annex III of Appendix 19 to the Rules of authorization of medicinal products, or when this has been agreed previously

with the competent authority (assessment organization) of the reference Member State respectively.

In addition, for medicinal products authorized in one Member State, the holder may also group several major variations of Type II affecting several marketing authorizations in a single Member State, or one or more major variation(s) of Type II with other minor variations affecting several marketing authorizations in a single Member State, provided that:

the variations are the same for all the marketing authorizations concerned,

the variations are submitted at the same time to the competent authority (assessment organization), and

the competent authority (assessment organization) has previously agreed to the grouping.

Furthermore, where the same major variation of Type II or the same group of variations (as explained above) affect several marketing authorizations owned by the same holder, the holder may submit these variations as one application for 'work-sharing'.

The application shall contain the elements listed in Annex IV to Appendix 19 to the Rules of authorization of medicinal products, presented as follows in accordance with the appropriate headings and numbering of the CTD format:

Cover letter.

The completed variation application form, including the details of the medicinal product concerned. Where a variation is the consequence of or related to another variation, a description of the relation between these variations should be provided in the appropriate section of the application form.

Reference to the variation code as laid down in the Annex V to Appendix 19 to the Rules of authorization of medicinal products, indicating that all conditions and documentation requirements are met or, where applicable, reference to a classification recommendation published in accordance with paragraph 1.5 of Appendix 19 to the Rules of authorization of medicinal products used for the relevant application.

Supporting data relating to the proposed variation(s).

Update or Addendum to quality summaries, non-clinical overviews and clinical overviews as relevant. When non-clinical or clinical study reports are submitted, even if only one, their relevant summary(ies) should be included in Module 2.

For variations requested by the competent authority resulting from new data submitted, e.g. pursuant to post-authorization conditions or in the framework of pharmacovigilance obligations, a copy of the competent authority (assessment organization) request should be annexed to the cover letter.

In case that the variations affect the summary of product characteristics, labelling, package leaflet or normative document: the revised product information (the summary of product characteristics, labelling, package leaflet) or normative document presented in the appropriate format, as well as the relevant translations into official languages of the Member States as required. Where the overall design and readability of the outer and/or immediate packaging is affected by the major variation of Type II, mock-ups should be provided to the competent authority (assessment organization).

For variations referred to in paragraph 1.1.3 of Appendix 19 to the Rules of authorization of medicinal products, the competent authority (assessment organization) of the reference Member State should additionally receive the list of dispatch dates indicating the appropriate type II variation procedure number, the dates on which the applications have been sent to each Member State concerned and confirmation that the fees for variation to the terms of the marketing authorization (and the assessment thereof) have been paid as required by the Member State concerned legislation.

For variations referred to in paragraph 1.1.4 of Appendix 19 to the Rules of authorization of medicinal products, confirmation that the fees for variation to the terms of the marketing authorization (and the assessment thereof) have been paid as required by the Member States legislation shall be provided to the competent authority (assessment organization) of the reference Member State.

2.3.2. Review of type II variations referred to in paragraph 1.1.3 of Appendix 19 to the Rules of authorization of medicinal products

The applicant shall submit to the competent authority (assessment organization) of the reference Member State an application in paper and/or electronic format as laid down in Appendix 2 to the Rules of authorization of medicinal products and confirmation that the relevant fees have been paid as required by the Member State legislation, as well as the dossier containing the elements referred to in paragraph 2.3.1 to these Rules.

Where needed and subject to agreement with the assessment organization, applicant shall submit samples of finished products, the reference standards of active substances and product-related impurities, specific reagents, and other materials necessary to carry out the laboratory testing to the competent authority (assessment organization) of the reference Member State.

The competent authority (assessment organization) of the reference Member State within 14 business days beginning with the day the variation application is submitted shall check completeness and accuracy of the format of the documents submitted.

If the application fulfils the requirements laid down in paragraph 2.3.1, the competent authority (assessment organization) of the reference Member State shall acknowledge receipt of a valid application.

The competent authority (assessment organization) of the reference Member State shall conclude the assessment of the medicinal product and draw up an assessment report within 60 calendar days following receipt thereof.

This period may be reduced by competent authority (assessment organization) of the reference Member State having regard to the urgency of the matter, or may be extended by the reference Member State to 90 days for variations concerning a change to or addition of therapeutic indications or for grouping of variations in accordance with paragraph 3.4.2(4) of Appendix 19 to the Rules of authorization of medicinal products.

The applicant shall be given a maximum of 90 calendar days which shall not be counted in the medicinal product assessment period and variation procedure to provide the missing materials to be included in the marketing authorization application dossier in response to the observations of the competent authority (assessment organization) of the reference Member State.

The competent authority (assessment organization) of the reference Member State shall refuse to accept the variation application in case of failure to submit the materials in response to the observations of the competent authority (assessment organization) of the reference Member State and/or if the payment of fees for the processing of a variation, as required by the reference Member State legislation, is not confirmed.

The competent authority (assessment organization) of reference Member State will prepare a draft assessment report and a decision on the application according to the communicated timetable and will circulate them to the concerned Member States for comments as well as to the applicant for information. The concerned Member States will send to the competent authority (assessment organization) of the reference Member State their comments within the deadlines set out in the timetable.

After receipt of the applicant’s response, the competent authority (assessment organization) of the reference Member State will finalize the draft assessment report and the decision on the application and will circulate them to the concerned Member States for comments as well as to the applicant for information.

2.3.3. Outcome of Type II variations assessment for mutual recognition procedure

By the end of the evaluation period, the competent authority (assessment organization) of the reference Member State will finalize and submit the assessment report and its decision on the application to the concerned Member States.

The competent authority (assessment organization) of the Member State concerned may send a request to the applicant and competent authority (assessment organization) of the reference Member State using the template provided in Appendix 18 to the Rules of

authorization and assessment of medicinal products within a maximum of 20 calendar days beginning with the day the access to the assessment report has been granted.

The period to response by the applicant to that request of the competent authority (assessment organization) of the Member State concerned and the reference Member State shall be a maximum of 90 calendar days. The period for providing requested documents by the applicant is not to be counted in the period of the assessment and processing of the variation.

If the applicant does not provide the documents or particulars requested by the competent authority (assessment organization) of the Member State concerned in due time, the assessment and the processing of the variation shall be terminated in that Member State concerned.

The applicant shall be informed in writing or electronically on that decision of the competent authority and/or assessment organization within 10 business days beginning with the day such a decision is made.

Within 30 calendar days following the receipt of the assessment report and decision of the competent authority (assessment organization) of the reference Member State, Member States concerned shall provide the opinion approvability of the assessment report drawn up by the competent authority (assessment organization) of the reference Member State unless a potential risk to human health is identified which prevents the competent authority (assessment organization) of the Member State concerned from approving the decision made by the reference Member State. Within 30 calendar days following the receipt of the final assessment report and opinion of the competent authority (assessment organization) of the reference Member State, the Member State concerned shall send its opinion to the reference Member State together with the exposition of the grounds for the negative decision (as the case may be) for not approving the assessment report drawn up by the reference Member State.

The competent authority (assessment organization) of the reference Member State shall refer the appropriate materials on the matters of disagreement to the Expert Committee for Medicinal Products at the Eurasian Economic Commission (hereinafter referred to as the Expert Committee) and shall notify the applicant and Member States concerned thereof. Where the competent authorities of one or more Member States concerned send an opinion not approving the assessment report drawn up by the assessment organization of the reference Member State, the Expert Committee shall carry out a procedure to resolve disagreement as laid down in the Rules of Procedure subject to approval by the Eurasian Economic Commission, within a maximum of 60 calendar days beginning with the day the Member States concerned send that opinion.

The competent authority of the reference Member State and relevant Member States concerned shall refuse to accept the variation where based on the outcome of the assessment of the medicinal product and upon completion of the procedure of resolving disagreement in the Expert Committee, the latter recommends refusing to accept the variation to the terms of the marketing authorization.

Where several Type II variations, or a group of Type II variation with other minor variations have been submitted as one application, the reference Member State will inform the applicant which variation have been accepted or rejected. The applicant may withdraw single variations from the grouped application during the procedure (prior to the finalization of the assessment by the reference Member State).

Following the positive decision made by the competent authority (assessment organization) regarding variations with changes to the summary of product characteristics, labelling or patient leaflet and normative document, the applicant shall submit translations of the summary of product characteristics, patient leaflet, mock-ups of the packaging as required by the Member State to all Member States concerned.

Where necessary, the competent authorities of the Member States concerned will update the marketing authorization within 60 calendar days following approval of the variation, provided that the documents necessary for the amendment of the marketing authorization have been submitted to the Member States concerned.

In the case of variations entailing amendments to product information as provided in paragraph 1.6 of Appendix 19 to the Rules of authorization of medicinal products, relevant competent authorities within 30 calendars days beginning with the day the decision is made, shall make publicly available the information on variations made in the Common Register together with the approved summary of product characteristics, medication guide, mock-ups of the packaging, normative document in accordance with the Procedure for establishing and maintaining the Common Register and shall issue the updated summary of product characteristics, medication guide, mock-ups of the packaging, normative document, certificate of the marketing authorization to the applicant, where necessary.

The accepted major variation of Type II can be implemented 30 days after the applicant has been informed about the acceptance of the variation by the reference Member State, provided that the necessary documents to amend the marketing authorization have been submitted to the Member State concerned. In those cases where the application has been the object of a referral to the Expert Committee, the variation must not be implemented until the referral procedure by the Expert Committee has concluded that the variation is accepted. However, the variations in the group not subject to the referral to the Expert Committee may be implemented if so indicated by the Member State.

Any variation entailing amendments to product information as provided in paragraph 1.6 of Appendix 19 to the Rules of authorization of medicinal products may be implemented once the marketing authorization is updated.

Variations related to safety issues must be implemented within a time-frame agreed between the reference Member State and the applicant.

2.3.4. Review of type II variations referred to in paragraph 1.1.4 of Appendix 19 to the Rules of authorization of medicinal products

The applicant shall submit to the competent authority (assessment organization) of the reference Member State an application in paper and/or electronic format as laid down in Appendix 2 to the Rules of authorization of medicinal products and confirmation that the relevant fees have been paid as required by the reference Member State legislation, as well as the dossier containing the elements referred to in paragraph 2.3.1 to these Rules.

Where needed and subject to agreement with the assessment organization, applicant shall submit samples of finished products, the reference standards of active substances and product-related impurities, specific reagents, and other materials necessary to carry out the laboratory testing to the competent authority (assessment organization) of the reference Member State.

The competent authority (assessment organization) of the reference Member State within 14 business days beginning with the day the variation application is submitted shall check completeness and accuracy of the format of the documents submitted in accordance with paragraph 2.3.1. If the application fulfils the requirements laid down in paragraph 2.3.1, the competent authority (assessment organization) of the reference Member State shall acknowledge receipt of a valid application.

The applicant shall be given a maximum of 90 calendar days which shall not be counted in the medicinal product assessment period and variation procedure to provide the missing materials to be included in the marketing authorization application dossier in response to the observations of the competent authority (assessment organization) of the reference Member State.

The competent authority (assessment organization) of the reference Member State shall refuse to accept the variation application in case of failure to submit the materials in response to the observations of the competent authority (assessment organization) of the reference Member State and/or if the payment of fees for the processing of a variation, as required by the reference Member State legislation, is not confirmed.

The competent authority (assessment organization) of the reference Member State shall conclude the assessment of the medicinal product and draw up an assessment report within 60 calendar days following receipt thereof.

This period may be reduced by competent authority (assessment organization) of the reference Member State having regard to the urgency of the matter, or may be extended by the reference Member State to 90 days for variations concerning a change to or addition of therapeutic indications or for grouping of variations in accordance with paragraph 3.4.2(4) of these Rules.

Within the assessment, the competent authority (assessment organization) may request the applicant in writing and/or electronically to provide supplementary information necessary to explain or clarify the documents or particulars provided in the marketing authorization application dossier (including proposals on amendments to the summary of product characteristics, medication guide, mock-ups of the packaging of the medicinal product, normative document or other documents of the marketing authorization application dossier).

The period to response by the applicant to that request should be a maximum of 90 calendar days.

The period for providing these documents requested by the competent authority or assessment organization by the applicant is not to be counted in the period of the assessment and processing of the variation.

If the applicant does not provide the requested documents or particulars in due time, the assessment and processing of the variation shall be terminated. The competent authority (assessment organization) of the reference Member State shall inform the applicant in writing or electronically on that decision within 10 calendar days beginning with the day such a decision is made.

2.3.5. Outcome of Type II variations referred to in paragraph 1.1.4 of Appendix 19 to the Rules of authorization of medicinal products

By the end of the evaluation period, the competent authority (assessment organization) will finalize the evaluation including its decision on the application and inform the applicant about the approval or rejection of the variation(s) (including the grounds for the unfavorable outcome).

Where several Type II variations, or a group of Type II variation with other minor variations have been submitted as one application, the competent authority (assessment organization) will inform the applicant which variation have been accepted or rejected. The applicant may withdraw single variations from the grouped application during the procedure (prior to the finalization of the assessment by the competent authority (assessment organization)).

After approval of the variation, the competent authority will, where necessary, amend the marketing authorization to reflect the variation within 60 calendar days provided that the documents necessary for the amendment of the marketing authorization have been submitted to the competent authority (assessment organization).

In the case of variations entailing amendments to product information as provided in paragraph 1.6 of Appendix 19 to the Rules of authorization of medicinal products, the competent authority of the reference Member State within 30 calendars days beginning with the day the decision is made, shall make publicly available the information on variations made in the Common Register together with the approved summary of product characteristics, medication guide, mock-ups of the packaging, normative document in accordance with the Procedure for establishing and maintaining the Common Register and shall issue the updated summary of product characteristics, medication guide, mock-ups of the packaging, normative document, certificate of the marketing authorization to the applicant, where necessary.

The accepted major variation of Type II can be implemented within 30 calendar days after the holder has been informed about the acceptance of the variation by the national competent authority, provided that the necessary documents to amend the marketing authorization have been submitted.

Any variation entailing amendments to product information as provided in paragraph 1.6 of Appendix 19 to the Rules of authorization of medicinal products may be implemented once the marketing authorization is updated.

Variations related to safety issues must be implemented within a time-frame agreed between the competent authority and the applicant.

2.4. Extensions

Annex I of Appendix 19 to the Rules of authorization of medicinal products sets out a list of changes to be considered as extensions. An application for an extension of a marketing authorization shall be evaluated in accordance with the same procedure as for the initial marketing authorization to which it relates as laid down in sections V and VI of Rules of authorization of medicinal products.

2.4.1. Submission of Extensions applications

Extension applications must be submitted to all Member States concerned, to the national competent authority, or to the Agency (as appropriate).

Holders may group under a single notification the submission of several extensions, or one or more extensions with one or more other variations, regarding the same marketing authorization provided that this corresponds to one of the cases listed in Annex III of Appendix 19 to the Rules of authorization of medicinal products, or when this has been agreed previously with the competent authority (assessment organization) of the reference Member State (as appropriate). However, no work-sharing of extensions applications is foreseen in Appendix 19 to the Rules of authorization of medicinal products.

The application must be presented as follows, in accordance with the appropriate headings and numbering of the CTD format:

Cover letter.

The completed application form.

Supporting data relating to the proposed extension.

A full Module 1 should be provided, with justifications for absence of data or documents included in the relevant sections of Module 1.

Update or Addendum to quality summaries, non-clinical overviews and clinical overviews as relevant. When non- clinical or clinical study reports are submitted, even if only one, their relevant summary(ies) should be included in Module 2.

In case that the extension affects the summary of product characteristics, labelling or package leaflet and normative document: the revised product information or normative document, presented in the appropriate format.

For extension applications in the procedure referred to in paragraph 1.1.3 of Appendix 19 to the Rules of authorization of medicinal products, the competent authority (assessment organization) of the reference Member State should additionally receive the list of dispatch dates indicating the procedure number, the dates on which the applications have been sent to each Member State concerned and confirmation that the relevant fees have been paid as required by the competent authorities concerned.

For extension applications in the procedure referred to in paragraph 1.1.4 of Appendix 19 to the Rules of authorization of medicinal products confirmation that the relevant fee has been paid as required by the competent authority (assessment organization).

2.4.2. Extension assessment for national procedure

An application for an extension of a marketing authorization shall be evaluated in accordance with the same procedure as for the initial marketing authorization to which it relates as laid down in sections V and VI of Rules of authorization of medicinal products.

2.5. Urgent Safety Restrictions

Paragraph 4.1.4 of Appendix 19 to the Rules of authorization of medicinal products foresees that in the event of a risk to public health in the case of medicinal products for human use or in the event of a risk to human health, the holder may take provisional ‘urgent safety restrictions’.

Urgent safety restrictions concern interim change in the terms of the marketing authorization due to new information having a bearing on the safe use of the medicinal product.

These urgent changes must be subsequently introduced via a corresponding variation in the marketing authorization.

The holder must immediately notify all Member States concerned of the restrictions to be introduced.

If no objections have been raised by the relevant authority within 24 hours following receipt of that information, the urgent safety restrictions are deemed accepted. They must be implemented within a time frame agreed between the competent authority (assessment organization) of the reference Member State and the holder.

The corresponding variation application reflecting the urgent safety restrictions (whether requested by the holder or imposed by the relevant authority) must be submitted by the holder as soon as possible within 14 business days.

Urgent safety restrictions may also be imposed by the competent authorities of the Member States (for nationally authorized medicinal products) in the event of a risk to public health in the case of medicinal products for human use.

III. PROCEDURAL GUIDANCE ON WORK-SHARING

Paragraph 4.1.2 of Appendix 19 to the Rules of authorization of medicinal products allows applicants to submit in one application the same Type IB, the same Type II variation, or the same group of variations corresponding to one of the cases listed in Annex III to Appendix 19 to the Rules of authorization of medicinal products or agreed with the competent authority (assessment organization) of the reference Member State (as appropriate) which does not contain any extension affecting:

more than one purely national marketing authorization of the same holder in more than one Member State; or

more than one marketing authorization of the same holder authorized in accordance with the Rules of authorization of medicinal products;

one or several purely national marketing authorization(s) of the same holder;

one or several purely national marketing authorization(s) and one or several marketing authorization(s) authorized in accordance with the Rules of authorization of medicinal products of the same holder.

In order to avoid duplication of work in the evaluation of such variations, a work-sharing procedure has been established under which one authority (the ‘reference authority’), chosen amongst the competent authorities of the Member States, will examine the variation on behalf of the other concerned authorities of the Member States.

A competent authority chosen by the Expert Committee, taking into account the recommendation of the applicant, will act as the reference authority.

In order to facilitate the planning of the procedure, holders are encouraged to inform the Expert Committee and the proposed reference authority in advance of the submission of a variation or group of variations to be subject to a work-sharing procedure.

In order to benefit from a work-sharing procedure, it is necessary that the same change(s) will apply to the different medicinal products concerned with no need (or limited need) for assessment of a potential product-specific impact. Therefore, where the ‘same’ change(s) to different marketing authorizations require the submission of individual supportive data for specific medicinal products concerned or separate product-specific assessment, such changes cannot benefit from work-sharing.

3.1. Submission of variation(s) application under work-sharing

A variation or group of variations presented for work-sharing must be submitted as explained in sections 2.2-2.3 of these Rules above and must be transmitted as one integrated submission package covering all variations for all medicinal products. This must include a common cover letter and application form, together with separate supportive documentation for each medicinal product concerned and revised product information (if applicable) for each medicinal product concerned. This will allow the competent authorities to update the dossier of

each marketing authorization included in the work-sharing procedure with the relevant amended or new information.

The work-sharing application must be submitted to all Member States where the products concerned are authorized.

3.2. Work-sharing assessment

When the applicant informs the Expert Committee of an upcoming work-sharing procedure, the Expert Committee will at the next meeting decide on the reference authority, taking into account the proposal of the applicant and, if applicable pursuant to paragraph 4.1.2 of Appendix 19 to the Rules of authorization of medicinal products, another relevant authority to assist the reference authority. Within 10 business days the applicant will be informed by the Expert Committee of the decision of which national competent authority will act as reference authority.

Upon receipt of a work-sharing application, the reference authority will handle the application as follows:

The reference authority will acknowledge receipt of a valid application for work-sharing. Immediately after acknowledging receipt of a valid application, the reference authority will start the procedure. The holder and the Member States concerned will be informed of the timetable at the start of the procedure.

As a general rule, work-sharing procedures will follow a 60-day period. This period may however be reduced by the reference authority having regard to the urgency of the matter, particularly for safety issues, or may be extended to 90 calendar days for variations concerning a modification of therapeutic indications or for grouping of variations in accordance with paragraph 1.7.2(4) or 3.4.2(4) of Appendix 19 to the Rules of authorization of medicinal products.

The reference authority will prepare an opinion according to the communicated timetable and will circulate it to the concerned Member States for comments as well as to the applicant for information. Concerned Member States will send their comments within the deadlines set out in the timetable.

Within the evaluation period, the reference Member State may request the applicant to provide supplementary information. The request for supplementary information will be sent to the applicant together with a timetable stating the date by when the applicant should submit the requested data (up to 90 calendar days) and, where appropriate, the extended evaluation period.

The procedure will be suspended until the receipt of the supplementary information. The assessment of responses may take up to 30 or 60 days depending on the complexity and amount of data requested to the applicant.

After receipt of the applicant’s response, the reference authority will finalize the draft opinion and will circulate it to the concerned Member States for comments as well as to the applicant for information.

3.3. Outcome of the work-sharing assessment

By the end of the evaluation period, the reference authority will issue its opinion on the application and inform the concerned Member States and the applicant.

In case of a favorable opinion, the list of variations that are not considered approvable should be attached in the Opinion (if applicable). Variations may be considered approvable for some of the concerned products only. In case of an unfavorable outcome, the grounds for the unfavorable outcome should be explained.

Within 30 days following receipt of the opinion, the concerned Member States will recognize the opinion and inform the reference Member State accordingly, unless a potential serious risk to public health or a potential serious risk to human or animal health is identified that prevents a Member State from recognizing the opinion of the reference Member State. The Member State that, within 30 days following receipt of the opinion of the reference Member

State, identifies such a potential serious risk should inform the reference Member State and give a detailed statement of the reasons for its position.

The reference authority will then refer the application to the Expert Committee to the matter of disagreement and will inform the applicant and the Member States concerned accordingly.

Where a referral to the Expert Committee is made, the procedure concerning the decision on the work-sharing application will be suspended until a decision has been adopted on the referral procedure by the Expert Committee.

After a positive opinion is communicated regarding variations with changes to the summary of product characteristics, labelling or package leaflet, the holder should submit, within 7 days, translations of the product information texts to all Member States concerned.

Within 30 days following the approval of the opinion or, where a referral has been triggered, the notification of the agreement of the Expert Committee, the Member States concerned will amend the marketing authorization accordingly, provided that the documents necessary for the amendment of the marketing authorization have been submitted to the Member States concerned.

Minor variations of Type IB approved via a work-sharing procedure, may be implemented upon receipt of the favorable opinion of the reference authority.

Any variation entailing amendments to product information as provided in paragraph 1.6 of Appendix 19 to the Rules of authorization of medicinal products may be implemented once the marketing authorization is updated.

Major variation of Type II (including those which contain grouped minor variations of Type IB) approved via a work-sharing procedure may be implemented 30 days after receipt of the favorable opinion from the reference authority provided that the necessary documentation to amend the marketing authorization has been submitted to the Member States concerned. In those cases where the application has been the object of a referral to the Expert Committee, the variation must not be implemented until the Expert Committee has concluded that the variation is accepted.

Variations related to safety issues must be implemented within a time-frame agreed between the reference authority and the holder.

APPENDIX 21
to the Rules of authorization
and assessment of medicinal
products for human use

TYPE I VARIATION TEMPLATE

Completion guide: preset text templates are bracketed in this document using < > and in italics; text template fragments to be filled by entering specific versions of the text on the specified property (parameter) are bracketed in curly brackets using {} with indication of the property (parameter) to be added in italics.

(template)

TYPE I VARIATION CRITICAL ASSESSMENT REPORT

Brand name of the medicinal product	
International non-proprietary name	
Strength(s)	
Pharmaceutical form	
Presentation	
Marketing authorization holder	

Rapporteur	
Date of this report	
Rapporteur	
Deadline for comments	

Administrative information

Reporter's contact person	Name: phone (fax) number: e-mail:
Names of the Rapporteur assessors (internal and external):	Quality: Name: Tel (fax): Email: Non-clinical: Name: Tel (fax): Email: Clinical: Name: Tel (fax): Email: Pharmacovigilance: Name: Tel (fax): Email:

1. Recommendations

Based on the review of the data on quality, safety, and efficacy, the assessor considers that the variation type in accordance with Appendices 19 and 20 to the Rules of authorization and assessment of medicinal products for human use (hereinafter referred to as the Rules) for <*medicinal product Brand name*> (<*INN*>), in the treatment of <*indication*>, for the following proposed change <*scope of variation*>,

<is approvable>;

<could be approvable provided that satisfactory answers are given to the "other concerns" as detailed in section 4 of this template>.

<is not approvable since "major objections" have been identified>.

[*Variation code in accordance with Appendix 19 to the Rules or variation section in accordance with Appendix 20 to the Rules shall be inserted for correct understanding of the scope of variation*]

Unprovable variation means that the major objections identified which preclude a recommendation for marketing authorization at the present time. The details of these major objections are provided below and should be addressed in writing and in an oral explanation using telephone. In addition, satisfactory answers must be given to the "other concerns" as detailed in section 4.

<In addition, the Rapporteur has recommended <conditions for marketing authorisation> <and> revisions to the proposed product information (see Appendix A).>

Apart from that, the reporter recommends the following conditions for the marketing authorization and changes of the proposed general characteristics of the medicinal product (see Annex A).

Grounds for refusal:

[Include grounds for non-acceptance in case of negative opinion]

2. Scientific discussion

2.1 Introduction

[Introduction – Brief statement on medicinal product and pharmacotherapeutic action. Rationale/background for the proposed change; if variation results from previous assessment request (e.g. FUM, PSUR) include summary of previous discussion and conclusion.

In general, the applicable section(s) and subheadings of the new MAA (renewal, variation application) AR template should be followed for the quality, nonclinical and clinical aspects. Information on the following parts should be included with subheadings as applicable:]

2.2. Quality aspects

2.3. Non-clinical aspects

2.3.1 Methods – analysis of data submitted
2.3.2 Results
2.3.3 Discussion

2.4 Clinical pharmacology aspects

2.4.1 Methods – analysis of data submitted
2.4.2 Results
2.4.3. Discussion

2.5. Clinical efficacy aspects

2.5.1. Methods – analysis of data submitted
2.5.2. Results
2.5.3 Discussion

2.6 Clinical safety aspects

2.6.1 Methods – analysis of data submitted
2.6.2 Results
2.6.3 Discussion

[In case of composite opinion on grouping and/or worksharing, the outcome of each variation in the group for each product should be reflected in the scientific discussion.]

2.7. Pharmacovigilance system

The assessors consider that the Pharmacovigilance system as described by the applicant fulfils the requirements the Rules of Good Pharmacovigilance Practice of the Eurasian Economic Union (hereinafter referred to as the Union) and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Eurasian Economic Union Member States (hereinafter referred to as the Member States) or in a third country.

The assessor considers that the Pharmacovigilance system as described by the applicant has the following deficiencies: <*list the deficiencies*>.

Provided that the deficiencies are rectified prior to the applicant placing the medicinal product on the market, the assessment organization may consider that the Pharmacovigilance system will fulfil the requirements. The applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.

2.8. Risk management plan

[The expert shall should have performed the first overall assessment of the application, together with identification of any major issues in the RMP (risk management plan). Where the competent assessment organization of the Member State established any divisions responsible for pharmacovigilance activities (hereinafter referred to as DRPA), their Advice it would be helpful for completing this section. This includes any particular nonclinical safety findings, gaps in the clinical pharmacology package, potential safety signals from the clinical trials, etc. At this stage it is particularly important that safety concerns are identified (important identified risks, important potential risks, important missing information). This is even more essential if these issues were not identified by the applicant in the dossier and are therefore unlikely to be reflected in the RMP.

This advice will in part be based on the assessments of the dossier by the assessor, hence the assessment reports for Modules 3 to 5 (see Appendices 6 to 8 to the Rules) will be an important source of information for the assessor.

Once the DRPA Advice is received, this will be integrated into the draft list of questions for discussion. It is important to note that this DRPA Advice may also contain proposed questions on the Risk Management Plan to be added to the assessment report. If the assessor deviates from the DRPA advice, then this will be discussed by the competent assessment organization.

Issues and/or concerns for consideration by the DRPA when assessing the RMP:

[Provide issues and concerns that were identified during the overall assessment of the application and that should be considered in the assessment of the Risk Management Plan by the DRPA.].

2.9.Changes to the summary of product characteristics

[Changes to the summary of product characteristics should be described presented as new text underlined and deleted text marked as strikethrough. However, if the changes are too extensive, changes to the concerned summary of product characteristics (SmPC) sections can be summarized and reference to the attachment can be made.]

The MAH proposed the following changes to the SmPC *<list the changes>:*

The Rapporteur requests <for the reasons discussed in detail above.> [refer to the scientific discussion above]/ <the following <additional> amendments to the Product Information: [Include brief description of the paragraphs where further amendments to the proposed changes are requested and the reasons for these requests.]

Changes were also made to the medication guide to bring it in line with the current version SmPC as laid down in the Requirements for the medication guide (patient leaflet) and summary of product characteristics of medicinal products for human use subject to approval by the Eurasian Economic Commission.

If user consultation results were submitted within this procedure, please discuss here as well.]

< The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet meets the criteria for readability as set out in the Requirements for the medication guide (patient leaflet) and summary of product characteristics of medicinal products for human use subject to approval by the Eurasian Economic Commission.> or

< The results of the user consultation with target patient groups on the package leaflet submitted by the MAH show that the package leaflet does not yet meet the criteria for readability as set out in the Requirements for the medication guide (patient leaflet) and summary of product characteristics of medicinal products for human use subject to approval by the Eurasian Economic Commission. The applicant will address the following minor issues concerning the user consultation with target patient group population on the package leaflet>.

or

< No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to <name(s) of product(s)>. The bridging report submitted by the applicant has been found <acceptable> <unacceptable>>.

[The latter is to be included if agreed by DRPA only.]

2.10. Direct healthcare professional communication

The assessor considers that a Direct Healthcare Professional Communication (DHPC) is needed to communicate on [insert brief summary of issue for communication].

[Details of target audience of DHPC to be summarised.]

The MAH should agree the translations and local specificities of the DHPC with competent authorities of the Member States. The DHPC should be sent [insert the agreed DHPC dissemination date] to [insert target audience].

[Following paediatric sections on significance and conformity only to be included if applicable for this variation]

2.11. The meaning of discrepancies in pediatric studies

[Attention! If confirmation of signal in children was observed for submission of this change, or if this submission includes pediatric studies mentioned in SPC, the appropriate guidelines in the area of pediatrics shall be used for evaluation of these changes.]

3. Overall conclusion and impact on the benefit/risk balance

[Include here a critical review of provided data underlining the variation request and its impact on the benefit risk balance of the product.

In a limited number of data that are considered as "key" to the benefit risk balance may be requested as a condition of the MA. In case issues have been identified for inclusion in Annex

B as conditions, use the following statement. Any measure identified as a condition needs to be well motivated in the AR, notably the need for a condition should be explained in the context of a positive benefit/risk balance.]

The assessor considers the following measures necessary:

<to address the nonclinical issues>

<to address the issues related to pharmacology>

<to address issues related to efficacy>

<to address issues related to pharmacovigilance>.

[In case of safety-related requests by the assessor (i.e. cumulative safety review to be submitted), please include the following sentence]

In addition, the assessor considered that the applicant should submit the following safety data <within X months> <the next PSUR>: *<list the data>*

[In case of composite opinion on grouping and/or worksharing, the outcome of each variation in the group for each product should be reflected in the scientific discussion.]

PSURs: Specify requirements only if different from the normal PSUR cycle.

The assessor recommends that the MAH will continue to submit <6 monthly> / <yearly> PSURs.

The marketing authorization holder shall submit periodic safety update reports for this product in accordance with the active substance INN.

The assessor's recommendation is subject to the following new conditions *<indicate the conditions>:*

The expert is of the opinion that the following obligation has been fulfilled, and therefore recommends its deletion from the Annex B:

Conditions or restrictions with regard to the safe and effective use of the medicinal product:

[Additional (beyond product literature) risk minimization activities to be fulfilled by the MAH should be listed here.

In case of additional risk minimization activities (e.g. controlled distribution, educational material, pregnancy prevention programs) are proposed beyond those addressed in the product information, these should be listed here and, as required to ensure correct implementation by the Member States, also in an Annex IV addressed to the Member States. Any exception to this rule (e.g. set up of surveillance programs in only a few MS) should be discussed and reflected in the AR].

Obligation to complete post-authorization measures

The MAH shall complete, within the stated timeframe, the following measures:

Description	Due date

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the member states:

[Actual risk minimization activities to be implemented by the Member States should be listed here. These should mirror the information under the section above, unless there are risk minimization activities specific to single Member States.

This annex should be provided for whenever there are 'Conditions or restrictions with regard to the safe and effective use of the medicinal product' specified in Annex B (e.g. controlled distribution, educational material, pregnancy prevention programs) that require Member States to ensure their correct implementation. Any exception to this rule (e.g. set up of

surveillance programs in only a few MS) should be discussed and reflected in the AR but not mentioned here].

Paediatric data

[Attention! If confirmation of signal in children was observed for submission of this change, or if this submission includes pediatric studies mentioned in SPC, the appropriate guidelines in the area of pediatrics shall be used for evaluation of these changes.]

4. Request for supplementary information

4.1. Major objections

[Definitions of questions

"Major objections", preclude a recommendation to the variation to the term of the marketing authorization. In principle, one major objection may entail more than one question and the use of bullet points or subheadings is encouraged. It is vital that the structure and content of a major objection are clear and understandable to the reader. Detailed comments may be necessary along with a reference to Union guidance documents.

Ideally, the objection should include a clarification as to what kind of response/action by the applicant could be considered to solve the problem.

"Other concerns", may affect the proposed conditions to the variation to the term of the marketing authorization and product information.

The wording of the objections and concerns should clearly provide the scientific rationale for the issues raised.

Quality aspects:

<Deficiencies arising from concerns over the confidential part of the Active Substance Master File are mentioned in separate annex of this report and not supplied to the MAH. These concerns will be conveyed in confidence to the holder of the Active Substance Master File.>

Non-clinical aspects:

Clinical aspects:

4.2. Other concerns

Quality aspects

Non-clinical aspects:

Clinical aspects:

5. Assessor's assessment of MAH responses to RSI

6. Updated overall conclusion and impact on the benefit-risk balance

[Include here an updated/consolidated critical review of provided data (initial submission and responses to RSI(s)) underlining the variation request and its impact on the benefit risk balance of the product.

Note regarding Obligation to complete post-authorization measures.

In a limited number of data that are considered as "key" to the benefit risk balance may be requested as a condition of the MA. In case issues have been identified for inclusion in Annex B as conditions, use the following statement. Any measure identified as a condition needs to be well motivated in the AR, notably the need for a condition should be explained in the context of a positive benefit/risk balance.]

The assessor considers the following measures necessary <to address the nonclinical issues> <to address the issues related to pharmacology> <to address issues related to efficacy> <to address issues related to safety>

[In case of safety-related requests by the assessor (i.e. cumulative safety review to be submitted), please include the following sentence:]

In addition, the Rapporteur considered that the applicant should submit the following safety data <within X months> <the next PSUR> *<list the required data>:*

[Note: in case of composite opinion on grouping and/or worksharing, the outcome of each variation in the group for each product should be reflected in the scientific discussion between competent assessment organization and DRPA. If a variation in the group has been withdrawn, it should also be reflected in the discussion.

PSURs: Specify requirements only if different from the normal PSUR cycle.]

The assessor recommends that the MAH will continue to submit <6 monthly> / <yearly> PSURs.

The marketing authorization holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union legal acts.

The assessor's recommendation is subject to the following new conditions *<list the conditions>:*

The assessor is of the opinion that the following obligation has been fulfilled, and therefore recommends its deletion from the Annex B.

7. Conditions or restrictions with regard to the safe and effective use of the medicinal product

[Additional (beyond product literature) risk minimization activities to be fulfilled by the MAH should be listed here.]

8. Obligation to complete post-authorization measures

The MAH shall complete, within the stated timeframe, the following measures connected to other (non-major) assessor's concerns:

Description	Due date

9. Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

[Actual risk minimization activities to be implemented by the Member States should be listed here. These should mirror the information under the section 7, but no included in full.

This section of the conclusion shall be included where the scope of actually fulfilled conditions or restrictions with regard to safe and efficacious use of the medicinal product in the Member State differs from the scope provided by the MA holder in the SPC.]

<Not applicable>

or

< These conditions do <fully><partly><not> reflect the advice received from the DRPA. <Divergences from the DRPA Advice are justified in an appendix to this report.>

or

< Divergent position(s) of DRPA to the majority recommendation <is><are> appended to this report.>

10. Pediatric data

[Attention! If confirmation of signal in children was observed for submission of this change, or if this submission includes pediatric studies mentioned in SPC, the appropriate guidelines in the area of pediatrics shall be used for evaluation of these changes.]

Annex A

The proposed annotated changes of SmPC, medication guide (PL), labeling with the assessor's comments after each section

Annex B

QRD guidance and checklist for the review of user testing results

Product information

Name of the medicinal product	
Name and address of the applicant	
Name of the company which has performed the user testing	
Type of Marketing Authorization Application	
INN	
Pharmacotherapeutic group (ATC Code)	
Therapeutic indications	
Orphan designation	☐ Yes ☐ No
Assessor	

Full user testing report provided ☐ Yes ☐ No
Summary report provided ☐ Yes ☐ No

Grounds for bridging testing based on a sound justification:
☐ extensions for the same route of administration
☐ ref to test on same class of medicinal product
☐ ref to test with same safety issues
☐ other (specify): _____

Is the justification for bridging acceptable? ☐ Yes ☐ No
(If no user testing report or summary report has been provided, a justification should be given).
Is the justification for not submitting a report acceptable? ☐ Yes ☐ No
(Examples of grounds that are not considered an acceptable justification for the lack of user testing are listed below:

- Administration in a hospital setting only;
- Administration by a healthcare professional only;
- Compliance with the QRD templates;
- Long established use of the product.

Reasons *[assessor's views on acceptability or not of the justification for not submitting user testing report or bridging form]*

_____
_____
_____

1. Technical assessment

1.1. Recruitment

Is the interviewed population acceptable? ☐ Yes ☐ No

Comments/further details

1.2. Questionnaire

Is the number of questions _____ sufficient? ☐ Yes ☐ No

Questions cover significant (safety) issues for the PL concerned? ☐ Yes ☐ No

Comments/further details: _____

1.3. Time aspects

Is the time given to answer acceptable? ☐ yes ☐ no

Is the length of interview acceptable? ☐ Yes ☐ No

Comments/further details _____

1.4. Procedural aspects

Rounds of testing including pilot _____

Comments/further details _____

1.5. Interview aspects

Was the interview conducted in well structured/organised manner? ☐ Yes ☐ No

Comments/further details _____

2. Evaluation of responses

2.1. Evaluation system

Is the qualitative evaluation of responses acceptable? ☐ Yes ☐ No

Does the evaluation methodology satisfy the minimum prerequisites? ☐ Yes ☐ No

Comments/further details _____

2.2. Question rating system

Is the quantitative evaluation of responses acceptable? ☐ Yes ☐ No

Comments/further details ☐ Yes ☐ No

3. Data processing

Are data well recorded and documented? ☐ Yes ☐ No

Comments/further details _____

4. Quality aspects

4.1. Evaluation of diagnostic questions

Does the methodology follow the Requirements for the medication guide (patient leaflet) and summary of product characteristics of medicinal products for human use subject to approval by the Eurasian Economic Commission? ☐ Yes ☐ No

Overall, each and every question meets criterion of 81% correct answers? ☐ Yes ☐ No

Comments/further details _____

4.2. Evaluation of the layout and design

Follows general design principles of the Requirements for the medication guide (patient leaflet) and summary of product characteristics of medicinal products for human use subject to approval by the Eurasian Economic Commission?☐ Yes ☐ No

Language includes patient friendly descriptions ☐ Yes ☐ No

Layout navigable ☐ Yes ☐ No

Use of diagrams acceptable ☐ Yes ☐ No

Comments/further details _____

5. Diagnostic quality/evaluation

Have any weaknesses of the PL been identified? ☐ Yes ☐ No

Have these weaknesses been addressed in the appropriate way? ☐ Yes ☐ No

Comments/further details

6. Conclusion

Have the main objectives of the user testing been achieved? ☐ Yes ☐ No

Is the conclusion of applicant accurate? ☐ Yes ☐ No

Overall impression of methodology ☐ Positive

Negative

Overall impression of leaflet structure ☐ Positive

Negative

Conclusion/Overview

APPENDIX 22
to the Rules of authorization
and assessment of medicinal products
for human use

NON-CLINICAL & CLINICAL ASPECTS – GENERIC MEDICINAL PRODUCTS TEMPLATE

Completion guide: preset text templates are bracketed in this document using < > and in italics; text template fragments to be filled by entering specific versions of the text on the specified property (parameter) are bracketed in curly brackets using {} with indication of the property (parameter) to be added in italics; explanations are given in italics in square brackets [ ].

(template)

CRITICAL ASSESSMENT REPORT
Non-clinical & clinical aspects – generic medicinal products

Rapporteur	
Co-rapporteur	
Start of the procedure:	
Date of this report:	
Deadline for comments:	

Administrative information

Application number:	
Brand name of the medicinal product:	
International Non-proprietary Name (INN) or common name of active substance(s):	
Applicant:	
Applied indications:	
Pharmaco-therapeutic group (ATC code):	
Dosage form and strength(s):	

Names of the Rapporteur assessors	Quality: Name: Tel (fax): Email: Non-clinical: Name: Tel (fax): Email: Clinical: Name: Tel (fax): Email:

List of abbreviations

1. Non-clinical assessment

<A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided [give a brief description of the overview]. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.>

<I believe that the non-clinical overview is based on up-to-date and sufficient data of literature review. There is no necessity to provide additional preclinical data.>

<I consider that the non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is not adequate because [give a comment].>

<A summary of the literature with regard to non-clinical data of {medicinal product} and justifications that the different <salt> <ester> <ether> <isomer> <mixture of isomers> <complex> <derivative> of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was <not>provided and was <not>accepted by the Union legal acts. This is <not> in accordance with the relevant guideline and additional non clinical studies were <not> considered necessary.>

Introduction

1.1 GLP aspects

1.2 Pharmacology

1.3 Pharmacokinetics

1.4 Toxicology

1.5 Conclusions on the non-clinical aspects

< There are no objections to approval of <trade name> from a non-clinical point of view.>

< As stated above, there are issues that need to be clarified, see list of questions.>

<I consider the following measures necessary to address the non-clinical issues: [list the required measures]:>

2. Clinical assessment

2.1 Introduction

< Relevant for the assessment <is><are> Rules for conducting bioequivalence studies of generic medicinal products of the Union, as well as [indicate other applicable legal acts and recommendations].>

The applicant did <not> receive Scientific Advice of the competent assessment organization pertinent to the clinical investigation.

This advice concerned the following topics: [provide summary]. The applicant did <not> follow this scientific advice.>

2.1.1. Compliance with the requirements of the Rules of the Good Clinical Practice of the Union

2.2. Biowaivers

2.3. Clinical pharmacology

2.3.1. Pharmacokinetics

< To support the application, the applicant has submitted <NUMBER> bioequivalence study(ies), <NUMBER> pharmacodymanic studies, <NUMBER > therapeutic equivalence studies.>

Tabular review of clinical studies

Study <Number>: <Title>
Methods
Study design: Assessor’s comment:
Test product and reference product: Assessor’s comment:
Population(s) studied: Assessor’s comment:
Analytical methods: Assessor’s comment:
Pharmacokinetic variables: Assessor’s comment:
Statistical methods: Assessor’s comment:

Results:

Table X

Pharmacokinetic parameters for <analyte> (non-transformed values)

Pharmacokinetic parameter	Test product		Reference product	
	<arithmetic> <geometric> mean	<SD> <CV%>	<arithmetic> <geometric> mean	<SD> <CV%>
<AUC(0-t)> <AUC(0-72h)>				
AUC(o-∞)				
^{C}max				
tmax				

<AUC_{0-t} area under the plasma concentration-time curve from time zero to t hours>
<$AUC_{0-72\ h}$ area under the plasma concentration-time curve from time zero to 72 hours>
$AUC_{0-\infty)}$ area under the plasma concentration-time curve from time zero to infinity "
C max maximum plasma concentration
T_{max} time for maximum concentration (* median, range)

Table X

Pharmacokinetic parameters for <analyte> (non-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence intervals	CV%*
<AUC(0-t)> <AUC(0-72 h)>			
^{C}max			

* estimated from the Residual Mean Squares

Assessor's comment:

Safety data:

Conclusions:

< Based on the presented bioequivalence study(ies) <(Brand) name> is considered bioequivalent with <reference product].>

or

< Due to the following reasons <elaborate on the reasons> <(Brand) name> is not considered bioequivalent with <reference product].>

Where applicable, the following statement may be used:

< The results of study <STUDY NUMBER> with <XX mg> formulation <CAN/CAN NOT> be extrapolated to other strengths <XX mg>, according to conditions in the Rules for conducting bioequivalence studies of generic medicinal products of the Union.>

2.3.2. Pharmacodynamics

<No new pharmacodynamic studies were presented and no such studies are required for this application.>

Assessor's comment:

2.3.3. Post marketing experience

<No post-marketing data are available. The medicinal product has not been marketed in any country.>

2.3.4. Discussion on clinical aspects

2.3.5. Conclusion on clinical aspects

<A summary of the literature with regard to clinical data of {medicinal product} and justifications that the different <salt><ester><ether><isomer><mixture of isomers><complex><derivative> of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was <not>provided and was <not>accepted by the competent authority. This is <not> in accordance with the relevant guideline and additional clinical studies were <not> considered necessary.>

<I consider the following measures necessary to address the clinical issues [list the measures required]:>

3. Pharmacovigilance

3.1. Pharmacovigilance system

<The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Union or in a third country has been provided.>

<I consider that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Union or in a third country.>

<I consider that the Pharmacovigilance system as described by the applicant has the following deficiencies: <list of deficiencies.>

<Provided that the deficiencies are rectified prior to the applicant placing the medicinal product on the market, the assessment organization may consider that the Pharmacovigilance system will fulfil the requirements. The applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.>

Assessor's comment:

3.2. Risk management plan

Issues and/or concerns for consideration by the pharmacovigilance assessor when assessing the RMP:

4. List of questions as proposed by the assessor

Non-clinical aspects:
Major objections:

<None.>
<Pharmacology>
<Pharmacokinetics>
<Toxicology>

Other concerns:

<None.>
<Pharmacology>
<Pharmacokinetics>
<Toxicology>

Clinical aspects:
Major objections:

<None.>
<Pharmacokinetics>
<Pharmacovigilance system>

<Risk management plan>

Other concerns:

<*None.*>
<Pharmacokinetics>
<Pharmacovigilance system>
<Risk management plan>

Recommendations:

5. Recommended conditions for marketing authorization and product information

6. Literature References

_____

APPENDIX 23
to the Rules of authorization
and assessment of medicinal products
for human use

GUIDANCE
on the content of critical assessment report for non-clinical and clinical aspects of generic medicinal products

This guidance is for the initial assessment of generic applications.

From a (non)clinical perspective, the primary basis for such assessment is usually the demonstration of bioequivalence. If, apart from bioequivalence studies, non-clinical data have been submitted for example to qualify impurities or to support the introduction of a new salt, a non-clinical assessment has to be performed. By analogy, additional clinical data may have been submitted (e.g. therapeutic equivalence studies) requiring a clinical assessment. In these cases, the template should be supplemented with relevant headings from the respective templates of the assessment report for full initial Marketing Authorization Applications.

Generic medicinal product is defined as having the same Qualitative and Quantitative composition in active substances and the same pharmaceutical form as a reference medicinal product and whose bioequivalence with the reference product has been demonstrated by appropriate bioequivalence studies.

The different salts, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of an active substance shall be considered to be the same active substance, unless they differ significantly in properties with regards to safety and/or efficacy. In such cases the, additional information providing proof of the safety and/or efficacy of the various salts, esters, or derivatives of an authorized active substance must be supplied by the applicant.

Also the purpose of an abridged application is to avoid the need for repetitive and unnecessary tests and trials.

Bioequivalence studies in humans may not be required if the applicant can demonstrate that the generic product meets relevant criteria for exemption as defined in Rules for conducting bioequivalence studies of generic medicinal products of the Eurasian Economic Union (hereinafter referred to as the Union).

1. Non-clinical assessment

For generic applications without non-clinical data

Consider the paragraph below if no new non-clinical data have been submitted.

<A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which. The overview justifies why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC are in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable. >

Provide the conclusion by using one of the following two options:

<I consider that the non-clinical overview is based on up-to-date and adequate scientific literature. It is agreed that no further non-clinical studies are required.>

< I consider that the non-clinical overview on the pre-clinical pharmacology, pharmacokinetics and toxicology is not adequate because [give a comment]>

If the second option is chosen, provide a detailed description of the missing information, the impact this lack of information has, and any potential requests for additional data. This should then be translated into the draft list of questions (section 4).

In case the generic contains a different salt, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the active substance, include the appropriate statement:

<A summary of the literature with regard to non-clinical data of {medicinal product} and justifications that the different <salt><ester><ether><isomer><mixture of isomers><complex><derivative> of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was <not>provided and was <not>accepted by the competent authority. This is <not> in accordance with the relevant guideline and additional non-clinical studies were <not> considered necessary.>

For generic applications including non-clinical data

New non-clinical data might exceptionally have been submitted to qualify impurities, to support the introduction of a new salt, or because new non-clinical data have become available in the framework of an update or by clinical experience, e.g. regarding pregnancy, lactation, QT, etc., which may impact the Summary of Product Characteristics (hereinafter referred to as SmPC). In such case a new nonclinical assessment has to be performed. Points of interest such as recently published and clinically relevant animal data presented in the overview may be stated and commented here if necessary.

Use the relevant headings (Pharmacology, Pharmacokinetics, Toxicology) from the template of the non-clinical assessment report for full initial Marketing Authorization Applications to describe such information. The below structure only provides the high-level headings; subheading should be added as appropriate. Also the assessment may have had an impact on the SmPC sections 4.6 and 5.3 (toxicology, mutagenicity, carcinogenicity, reproductive toxicity: teratogenicity, pregnancy, breastfeeding), which should be reflected hereunder.

1.5. Conclusions on non-clinical aspects

In case new non-clinical data was provided conclude on these data.

State if the SmPC of the generic product is identical to the reference product. Normally it should be, but any differences should be mentioned here. State whether the differences are justified or not.

State those issues that need to be clarified. These should be carried forward to the benefit risk assessment in the Clinical part of this report, and listed in the List of Questions as appropriate.

Provide the conclusion by using one of the following two options:

<There are no objections to approval of <trade name> from a non-clinical point of view.>

or

<As stated above, there are issues that need to be clarified, see list of questions.>

Obligation to complete post-authorization measures: In case nonclinical issues have been identified for inclusion in SmPC as conditions. Any measure identified as a condition needs to be well motivated, notably the need for a condition should be explained in the context of a positive benefit/risk balance:

<I consider the following measures necessary to address the non-clinical issues:>

2. Clinical assessment

2.1. Introduction

Describe the Product profile: Indications and dosage (SmPC sections 4.1 and 4.2), pharmacodynamics and pharmacokinetics of the active substance PK summary of substance and formulation; absorption, distribution, metabolism, elimination data of special interest in respect of bioequivalence studies (linearity, elimination time etc.)(see e.g. text books such as Goodman & Gilman, Martindale etc.)

Relevant for the assessment <is><are> Rules for conducting bioequivalence studies of generic medicinal products of the Union, as well as [indicate other applicable legal acts and recommendations>.

< The applicant did <not> receive Scientific Advice of the competent assessment organization pertinent to the clinical investigation.

< This advice concerned the following topics: [provide summary]. The applicant did <not> follow this scientific advice.>

2.1.1. Compliance with the requirements of the Rules of the Good Clinical Practice of the Union

Compliance with the Rules of the Good Clinical Practice of the Eurasian Economic Union subject to approval by the Eurasian Economic Commission should be addressed here and in section 3.1 and also in the overview assessment report on safety, quality, and efficacy

In this section specifically address:

Any concerns raised during the assessment about compliance with Good Clinical Practice or related regulatory and ethical requirements (data accuracy or protocol compliance and compliance with ethical aspects).

Statement on application of ethical standards in clinical trials foreseen by the Rules of the Good Clinical Practice of the Union;

Discuss the need for an inspection for compliance with the Rules of the Good Clinical Practice based on the Rules of authorization and assessment.

Decision on inspection shall be maid based on several critical factors as laid down in the Rules taking into account the application as a whole. The list of critical factors is non-exhaustive; significance of each factor for making a decision on unscheduled inspection for compliance with the Rules of the Good Clinical Practice of the Union may largely depend on various parameters.

For detailed information on inspection triggers, see the Rules and Rules of carrying out of pharmaceutical inspections of the Union.

To trigger an inspection for compliance with the requirements of the Good Clinical Practice of the Union, you need to:

Contact your national pharmaceutical inspectorate.

Determine with them the clinical trial(s), sites and special concerns or issues to be addressed/the trigger or random factor related to the inspection.

Formulate the formal inspection request for review by the inspectors and agreement by the competent assessment organizations of the Member States for adoption by the competent assessment organization of the Member States of the Union and inclusion in the inspection plan (day 90 or 120 of the granting a marketing authorization).

2.2. Biowaiver

In this section describe two different kinds of biowaiver:

exemption for strength(s);

BCS-based Biowaiver.

Refer to the respective requirements of the Rules for conducting bioequivalence studies of generic medicinal products of the Union.

Also this section should be used to justify an exemption from the requirement to perform bioequivalence studies for e.g. certain dosage forms in accordance with the abovementioned guideline.

2.3. Clinical pharmacology

2.3.1. Pharmacokinetics

To support the application, the applicant has submitted <number> bioequivalence study(ies), <number> pharmacodymanic studies, <number > therapeutic equivalence studies.

State the reasons for submitting more than one bioequivalence trial. If there is more than one clinical study, each of them should be described separately using the below structure.

Table 1.

Tabular overview of clinical studies

Study <number>: <title>

Methods

Study design

Detailed description of the study design including drug intake procedures (fasting state or with food), wash-out time, meals served fed/fasted condition, constituents of meal (in fed studies), multiple/single dose, applied dose, wash-out period, blinding, crossing-over, randomization, sampling schedule, analyzed compound (parent and/or metabolites) and matrix (plasma, urine data).

In case of a steady-state study, relevant details (multiple dosing).

Information about investigator, study site, protocol number, study duration, bioanalysis facility, biostatistician and/or biostatistical institute.

Assessor's comment

Critical assessment of the adequateness of the study design.

Test and reference medicinal products

Detailed information of the reference product (name) strength, pharmaceutical form, MAH, date of authorization in the Union and the detailed information (such as MA batch number and country of origin) of the batches used in the studies need to be provided in tabular format.

The following information should be included: Actual strength vs. nominal strength of the test and reference products employed in the bioequivalence study, batch size of the test product employed in the bioequivalence study and commercial batch size.

Assessor's comment

The assessment should address if required data were given, if the test product is identical to the formulation intended to be marketed.

Population(s) studied

Description of number of subjects included in the study, number of subjects included in PK- and statistical analysis, drop-outs (reason why in detail), ethnicity, gender, age, health status, etcetera

Assessor's comment

The assessment should address if populations chosen is according to guidelines, inclusion/exclusion criteria ok, sample size calculation ok, ethnicity, gender, age, health status, etc. Assess potential protocol deviations/violations.

Analytical methods

Detailed description of analytical methods used, with emphasis on the performance characteristics of assay validation and quality control.

Provide all details relevant for the assessment of the validity of the bioanalytical method in accordance with the Rules for conducting bioequivalence studies of generic medicinal products of the Union.

Assessor's comment

Address if the analytical method acceptable, validated, handling of samples adequate. Assess potential protocol deviations/violations.

Pharmacokinetic variables

Summaries pharmacokinetic variables and their generation (Non-compartmental/compartmental, PK analysis software. Choice of primary and secondary variables)

Assessor's comment

Assess if pharmacokinetic variables and methods were adequate.

Statistical methods

Description of statistical methods including prospectively defined acceptance criteria.

Assessor's comment

Assess if the statistics described were adequate, methods acceptable (transformations, parametric tests, handling of missing values, outliers, basis of bioequivalence, whether there were protocol deviations/violations and if any widening of the acceptance criteria has been adequately justified).

Results

Summaries the relevant data for the bioequivalence assessment in the below tables rather than copying detailed statistical outputs from the clinical study report.

Table X Pharmacokinetic parameters for <analyte>

(non-transformed values)

Pharmacokinetic parameter	Test		Reference	
	<arithmetic> <geometric> mean	<SD> <CV%>	<arithmetic> <geometric> mean	<SD> <CV%>
<$AUC_{(0–t)}$> <$AUC_{(0–72\ h)}$>				
$AUC_{(0–\infty)}$				
C_{max}				
T_{max}*				

<$AUC_{0–t}$	area under the plasma concentration-time curve from time zero to t hours>
<$AUC_{0–72\ h}$	area under the plasma concentration-time curve from time zero to 72 hours>>
$AUC_{0–\infty}$	area under the plasma concentration-time curve from time zero to infinity
C_{max}	maximum plasma concentration
T_{max}	time for maximum concentration (* median, range)

Table X Statistical analysis for <analyte>

(ln-transformed values)

Pharmacokinetic parameter	Geometric Mean Ratio Test/Reference	Confidence Intervals	CV%*
<$AUC_{(0–t)}$> <$AUC_{(0–72\ t)}$>			
C_{max}			
* estimated from the Residual Mean Squares			

In case steady state studies have been performed, similar tables should be produced reporting the parameters $AUC_{0-\tau}$, C_{max}, C_{min}, and fluctuation index (PTF%).

Assessor's comment

Safety data

Provide a very brief summary of the adverse events observed in the bioequivalence study. No conclusion in terms of comparison between test and reference should be made based on these data.

Conclusions

<Based on the presented bioequivalence study(ies) <(Brand) name> is considered bioequivalent with <reference product>.

or

<Due to the following reasons < elaborate on the reasons > <(Brand) name> is not considered bioequivalent with <reference product>.

If applicable;

The results of study <study number> with <XX mg> formulation <can/cannot> be extrapolated to other strengths <XX mg>, according to conditions in the Rules for conducting bioequivalence studies of generic medicinal products of the Union.

2.3.2. Pharmacodynamics

<No new pharmacodynamic studies were presented and no such studies are required for this application.>

If applicable, usually no new data required and given. Required, if bioequivalence cannot be shown by pharmacokinetic studies in order to substantiate therapeutic equivalence.

2.3.3. Post marketing experience

Consider any evaluation of the safety data submitted (if the product has already been on the market elsewhere outside the Union). However this is rarely available; Note that this information relates to the medicinal product and not the active substance.)

The following case is more likely:

<No post-marketing data are available. The medicinal product has not been marketed in any country.>

2.3.4. Discussion on clinical aspects

Discuss critical design elements particularly if different from the standard cross-over design, e.g. parallel design, fed versus fasting state, investigation in patients, etc. Any relevant of

the analyte (parent versus metabolite) as well as the bioanalytical method should be discussed. Also reflect on the pre-specified acceptance criteria for bioequivalence, particularly if scaling is applied for highly variable drugs (e.g. has a replicate design been employed to estimate the CV?) or for narrow therapeutic index drugs.

For the results, state whether the pre-set bioequivalence criteria where met. Also summarize any issues with regard to the conduct of the study (e.g. withdrawals/replacement of subjects). In case of conduct of more than study against the reference product, assess the conclusiveness of the available data.

Any concerns with regard to the GCP compliance of the study should be clearly described and discussed.

2.3.5. Conclusions on clinical aspects

Conclude on clinical aspects and carry forward open issues to the list of questions.

In case the generic contains a different salt, esters, ethers, isomers, mixtures of isomers, complexes or derivatives of the active substance, include the appropriate statement:

<A summary of the literature with regard to clinical data of {medicinal product} and justifications that the different <salt><ester><ether><isomer><mixture of isomers><complex><derivative> of the active substance does not differ significantly in properties with regards to safety and efficacy of the reference product was <not>provided and was <not>accepted by the competent authority. This is <not> in accordance with the relevant Union requirements and additional clinical studies were <not> considered necessary.>

Obligation to complete post-authorization measures: In a limited number of cases in the context of a standard MA clinical data that are considered as “key” to the benefit risk balance may be requested as a condition of the MA. In case clinical issues have been identified for inclusion in SmPC as conditions, use the following statement. Any measure identified as a condition needs to be well motivated, notably the need for a condition should be explained in the context of a positive benefit/risk balance:

<I consider the following measures necessary to address the clinical issues:>

3. Pharmacovigilance

3.6. Pharmacovigilance system

<The applicant has provided documents that set out a detailed description of the system of pharmacovigilance. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country has been provided. >

<I consider that the Pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the notification of any adverse reaction suspected of occurring either in the Union or in a third country.>

< I consider that the Pharmacovigilance system as described by the applicant has the following deficiencies: <list of deficiencies.>

<Provided that the deficiencies are rectified prior to the applicant placing the medicinal product on the market, the assessment organization may consider that the Pharmacovigilance system will fulfil the requirements. The applicant must ensure that the system of pharmacovigilance is in place and functioning before the product is placed on the market.>

3.7. Risk management plan

The assessor should have performed the first overall assessment of the application, together with identification of any major issues in the RMP. It is recommended to flag any particular issues and concerns that were identified during the assessment of the dossier that could impact the Risk Management Plan. This includes any particular nonclinical safety findings, gaps in the clinical pharmacology package, potential safety signals from the clinical trials, etc. At this stage it is particularly important that safety concerns are identified (important identified risks, important potential risks, important missing information). This is even more essential if these issues were not identified by the applicant in the dossier and are therefore unlikely to be reflected in the RMP.

Issues and/or concerns for consideration by the assessor when assessing the RMP:

Provide issues and concerns that were identified during the overall assessment of the application and that should be considered in the assessment of the Risk Management Plan by the pharmacovigilance officer.

4. List of questions as proposed by the assessor

“Major objections”, preclude a recommendation for marketing authorization. In principle, one major objection may entail more than one question and the use of bullet points or subheadings is encouraged. It is vital that the structure and content of a major objection are clear and understandable to the reader. Detailed comments may be necessary along with a reference to guidance documents.

Ideally, the objection should include a clarification as to what kind of response/action is expected from the applicant.

“Other concerns”, may affect the proposed conditions for marketing authorization and product information. Other concerns should be resolved before approval: failure to do so may render the application un-approvable.

This list should be carried forward to the overview assessment report on safety, quality, and efficacy.

5. Recommended conditions for marketing authorization and product information

6. List of references

Appendix No. 24
to the Rules for the Marketing Authorisation
and Evaluation of Medicinal Products
for Human Use

REQUIREMENTS
FOR THE PROCEDURE FOR MAKING AMENDMENTS TO THE MASTER FILE OF SEASONAL, PANDEMIC AND PRE-PANDEMIC (ZOONOTIC) VACCINES IN CASE OF CHANGES IN THE STRAIN COMPOSITION OF INFLUENZA VACCINES, AS WELL AS MARKETING AUTHORISATION OF SEASONAL, PANDEMIC AND PRE-PANDEMIC (ZOONOTIC) INFLUENZA VACCINES

(introduced by Decision of the Council of the Eurasian Economic Commission No. 55 dated 14.06.2018)

I. General Provisions

These Requirements apply to the procedures for the marketing authorisation of influenza vaccines and define the unified procedure for making amendments to the master file of seasonal, pandemic and pre-pandemic (zoonotic) vaccines in case of changes (update) in the strain composition of influenza vaccines according to the 'fast track' procedure, as well as marketing authorisation of seasonal, pandemic and pre-pandemic (zoonotic) influenza vaccines on the customs territory of the Eurasian Economic Union (hereinafter referred to as the Union).

The Requirements are inextricably linked to the Rules for conducting studies of biological medicinal products of the Eurasian Economic Union, approved by the Decision of the Council of the Eurasian Economic Commission No. 89 Dated November 3, 2016).

The Requirements do not apply to the amendments not connected with the changes (update) in the strain composition of seasonal, pandemic and pre-pandemic (zoonotic) influenza vaccines.

II. Definitions

For the purposes of the Requirements, the used definitions mean the following:

a pandemic preparedness vaccine is a candidate influenza vaccine (or a technology of vaccine development) developed for the purpose of immunisation of people in case of influenza caused by pandemic influenza strains;

a pandemic vaccine is an influenza vaccine intended for immunisation of people in case of influenza caused by pandemic influenza strains;

a pre-pandemic (zoonotic) vaccine is an influenza vaccine intended for immunisation of people in case of flu outbreaks caused by zoonotic influenza strains;

a seasonal vaccine is a vaccine against influenza intended for immunisation of people in case of influenza caused by epidemic influenza strains;

a competent authority (an expert organisation) of a reference state or a Member State concerned is an authorised body of a Member State of the Union in the field of circulation of medicinal products, which is authorised to conduct marketing authorisation, confirmation of marketing authorisation (re-registration), to make amendments in the master file or other procedures related to the marketing authorisation of medicinal products for human use and provided for in the Rules for the marketing authorisation and evaluation of medicinal products for human use, established in Decision of the Council of the Eurasian Economic Commission No. 78 dated November 3, 2016 (hereinafter referred to as the Rules).

III. Regulatory and Procedural Requirements for the Marketing Authorisation of Vaccines and Making Changes in Strain Composition of Influenza Vaccines

1. Seasonal influenza vaccines

1.1. Requirements for the marketing authorisation application for influenza vaccines

The marketing authorisation application for a new seasonal influenza vaccine shall be accompanied with a set of documents in accordance with Appendix No. 1 to the Rules.

1.2. Requirements for the application to change the strain composition of seasonal influenza vaccines

The applicant shall have the right to submit the application to change the strain composition of a seasonal influenza vaccine after formal notice of a competent authority (expert organisation) of the Member State of the Union (hereinafter referred to as the Member State) on the start of acceptance of applications after the publication of annual recommendations of the World Health Organisation (WHO) about vaccination against influenza and until the deadline determined by the competent authority (expert organisation) of the reference state. When submitting the application, it is necessary to follow the provisions of Appendices No. 2, 19 and 20 to the Rules.

Please specify the following in the table column "Amendment name" in paragraph 2 "Introduced amendments" of form III of the application to change the master file of a drug product (Appendix No. 2 to the Rules): annual update of the strain(s) of an influenza vaccine. The application shall be submitted under the change procedure II, type Б.I.a.5 (in accordance with Appendix No. 19 to the Rules).

For the purpose of an annual update of the strain(s) of an influenza vaccine by way of derogation from the provisions provided for in subsections 2.3 and 3.3 of Appendix No. 19 to the Rules, the described below procedure for evaluation of changes affecting the changes in the active drug substance is applied.

Under this procedure, the applicant is not allowed to make any amendments, and competent authorities (expert organisations) of a reference state and Member States concerned are not allowed to require making any amendments to the master file of an influenza vaccine, except for the amendments made due to the change in strain composition. The changes not associated with the emergence of new strains are made in accordance with Sections II and III of Appendix No. 19 and Appendix No. 20 to the Rules.

Prior to submitting an application to change strain composition of a vaccine, the applicant shall have the right to apply in advance to a competent authority (expert organisation) of a reference state with a request for conducting scientific and pre-authorisation consultations to plan an evaluation procedure for the amendments made, including without limitation possible deviation from the term stipulated in this procedure.

1.3. Selection of epidemically relevant influenza strains for the use in the composition of seasonal influenza vaccines

Prior to each coming epidemic season, it is allowed to make annual changes in the composition of authorised seasonal influenza vaccines in order to update strain(s) according to the WHO recommendations. When predicting influenza epidemic with the circulation of influenza virus strains not recommended by the WHO, the Member State shall have the right to make changes in the master file of influenza vaccines on the basis of the decision of a competent authority of the Member State or Member State committee on influenza.

Twice a year (typically in February or March for the northern hemisphere and in September for the southern hemisphere) the WHO experts recommend the influenza A and B virus strains that should be used in the production of seasonal influenza vaccines for the coming season.

1.4. The description of a procedure

1.4.1. The procedure for making changes in the master file of an influenza vaccine (update of seasonal strain composition) in the reference state

A competent authority (expert organisation) of the reference state shall evaluate the sufficiency, completeness and accuracy of the submitted documents of the master file of influenza vaccines and send the application and the master file of influenza vaccines to the expert organisation of the reference state (master file for update) within 5 business days from the date of submission of the application to change the master file of influenza vaccines.

If the application and the master file of influenza vaccines comply with Section 5 of the Requirements, the competent authority (expert organisation) of the reference state shall initiate the procedure for making changes in the master file of influenza vaccines and inform the applicant about it. The procedure period shall not exceed 40 calendar days.

An expert organisation of the reference state shall carry out an examination of the master file of influenza vaccines within 25 calendar days from the date of notification of the applicant of initiating the procedure to make changes in the master file of influenza vaccines. After the evaluation procedure, the expert organisation of the reference state shall draw up a report on safety, efficacy and influenza vaccine quality evaluation (hereinafter referred to as the evaluation report).

The expert organisation of the reference state shall have the right to request additional data necessary to carry out the evaluation from the applicant within 25 calendar days from the date of notification of the applicant of initiating the procedure to make changes in the master file of influenza vaccines.

When the request is received from the competent authority (expert organisation) of the reference state, the applicant shall provide additional date within 7 business days. The time given to the applicant to respond to the above-mentioned request shall not be included in the total period necessary for carrying out the procedure and specified in paragraph two of this subsection. After the receipt of the requested additional data, the competent authority (expert organisation) of the reference state shall resume the evaluation procedure.

The expert organisation of the reference state shall carry out the evaluation of the additional data, provided by the applicant, within the period not exceeding 5 business days.

Within 1 business day from the date of drawing up an expert report, the expert organisation of the reference state shall send this report to the applicant.

Within 2 business days, the competent authority of the reference state shall make a decision on authorisation or refusal to change the master file of influenza vaccines on the basis of the expert report on evaluation drawn up by the expert organisation of the reference state.

1.4.2. The procedure for making changes in the master file of an influenza vaccine (update of seasonal strain composition) in the Member State concerned

The applicant shall also submit to the competent authorities (expert organisations) of the concerned Member States the application to change the strain composition of an influenza vaccine in hard copy and electronic form according to Appendix No. 2 to the Rules, as well as documents confirming the payment of the fee (charges) for making amendments to the master file of influenza vaccines in cases stipulated in the legislation of the concerned Member States.

The competent authority (expert organisation) of the reference state shall inform the competent authorities (expert organisations) of the concerned Member States and the applicant about the start of the procedure for making amendments to the master file of influenza vaccines in the reference state or about the refusal to carry out this procedure via the integrated information system of the Union (hereinafter referred to as the integrated system).

Within 2 business days from the date of receipt of the notification of the start of the procedure for making amendments to the master file of influenza vaccines by the competent authorities (expert organisations) of the concerned Member States, the competent authority (expert organisation) of the reference state shall grant access to the documents included in the master file of influenza vaccines via the integrated system.

The competent authority (expert organisation) of the concerned Member State shall evaluate the sufficiency, completeness and accuracy of the submitted documents in accordance with the legislation of its own state and start the procedure for making amendments to the master file of influenza vaccines within the period not exceeding 5 business days from the date of receipt of the access to the documents included in the master file of influenza vaccines. The period for carrying out this procedure shall not exceed 40 calendar days from the date of submission of the application to change the master file of influenza vaccines.

The competent authority (expert organisation) of the reference state shall prepare a draft expert report on evaluation and grant access to it to the competent authorities (expert organisations) of the concerned Member State via the integrated system within 25 days calendar days from the date of notification of the applicant of the procedure start in the reference state.

The competent authority (expert organisation) of the concerned Member State shall send the comments on the draft expert report on evaluation to the competent authority (expert organisation) of the reference state within 1 business day from the date of access granting.

The competent authority (expert organisation) of the reference state shall make amendments to the expert report on evaluation taking into account the received comments from the competent authorities (expert organisations) of the concerned Member States and shall grant the competent authority (expert organisation) of the concerned Member State access to the expert report on evaluation with the amendments made via the integrated system.

The competent authority (expert organisation) of the reference state shall have the right to request additional data necessary to carry out the evaluation from the applicant taking into account the comments received from the competent authorities (expert organisations) of the concerned Member States and shall inform the applicant and the competent authorities (expert organisations) of the concerned Member States about it via the integrated system or by any other means.

The applicant shall send the request response to the competent authority (expert organisation) of the reference state within 7 business days from the date of the request receipt from the competent authority (expert organisation) of the reference state. The time given to the applicant to respond to the above mentioned request shall not be included in the total time period necessary for carrying out the procedure for making amendments to the master file of an influenza vaccine.

The competent authority (expert organisation) of the reference state shall inform the competent authorities (expert organisations) of the concerned Member States about resuming the procedure for making amendments to the master file of influenza vaccines and shall grant them access to the data requested within 2 business days from the date of receipt of such data by the competent authority (expert organisation) of the reference state.

The competent authority (expert organisation) of the reference state shall prepare a draft expert report on evaluation taking into account the additional data submitted by the applicant and shall grant access to it to the competent authorities (expert organisations) of the concerned Member States within 5 business days from the date of resuming the evaluation in the reference state via the integrated system.

The competent authority (expert organisation) of the concerned Member State shall make a decision on making amendments to the master file of influenza vaccines or on refusal to change it within 2 business days from the date of granting access to the expert report to the competent authorities (expert organisations) of the concerned Member States and shall inform the applicant and the competent authority (expert organisation) of the reference state about the decision via the integrated system or by any other means.

After the competent authorities (expert organisations) of the reference state and the concerned Member State make a decision on making amendments to the master file of influenza vaccines and receive the corresponding notification, the applicant shall submit the translation of the general description of the drug product, package insert, package design of an influenza vaccine into the official languages of the reference states and the concerned Member States (if there is a corresponding requirement in the legislation of the reference state and the concerned Member States) within 7 business days from the date of the receipt of the notification by the applicant.

The competent authority (expert organisation) of the reference state shall inform the applicant of the decision on making amendments to the master file of influenza vaccines and shall issue new marketing authorisation documents within the period not exceeding 40 calendar days from the date of the start of carrying out the procedure for making amendments to the master file of influenza vaccines or within the period not exceeding 10 calendar days from the date of resuming the specified procedure after the applicant submits the response to the request on the provision of additional data necessary for completing the evaluation of the master file of influenza vaccines.

The competent authorities (expert organisations) of the concerned Member States shall inform the applicant of the decision on making amendments to the master file of influenza vaccines and shall issue new marketing authorisation documents within the period not exceeding 40 calendar days from the date of the start of carrying out the procedure for making amendments to the master file of influenza vaccines or within the period not exceeding 10 calendar days from the date of resuming the specified procedure after the applicant submits the response to the request on the provision of additional data necessary for completing the evaluation of the master file of influenza vaccines (if the applicant submits documents necessary for making amendments to the master file of influenza vaccines).

The competent authorities (expert organisations) of the concerned Member States shall place information on making amendments to the master file of influenza vaccines and update documents of the master file of influenza vaccines in the unified register of the authorised medicinal products with the help of the integrated system.

In case of the expert report with unfavourable findings on the basis of which the competent authority (expert organisation) of the reference state will make a decision on the refusal to make amendments to the master file of an influenza vaccine, the specified competent authority (expert organisation) shall inform the applicant about it by e-mail or in the written form within 10 business days from the date of making this decision.

2. Pre-pandemic (zoonotic) influenza vaccines

2.1. Requirements for the marketing authorisation application for a pre-pandemic (zoonotic) influenza vaccine

The application for marketing authorisation of a pre-pandemic (zoonotic) influenza vaccine shall be submitted to the competent authority (expert organisation) of the reference state in accordance with section I and subsection 12.2 of section III of Appendix No. 1 to the Rules.

2.2. Requirements for the application to change the strain composition of a pre-pandemic (zoonotic) influenza vaccine

The application to change the strain composition of a pre-pandemic (zoonotic) influenza vaccine shall be submitted in the form of an amendment to the master file. The specified amendment is classified as type II according to subsection Б.I.a.5 of Appendix No. 19 to the Rules.

3. Pandemic influenza vaccines and pandemic preparedness vaccines

3.1. Requirements for the marketing authorisation application for a pandemic preparedness vaccine

In order to prepare for a pandemic situation, applicants shall submit a marketing authorisation application for a candidate pandemic vaccine containing a virus strain with pandemic potential (pandemic preparedness vaccine).

This type of vaccine is based on the concept known as a mock-up vaccine concept. According to this procedure, a newly registered pandemic preparedness vaccine and a mock-up vaccine will have the following same characteristics:

manufacturing parameters;

preparation technology;

vaccine composition, including the content of an antigen, excipients, an adjuvant (if necessary) and other components (except for the strain(s));

specification parameters and pandemic preparedness vaccine quality control methods.

When an influenza pandemic situation is duly recognised by the WHO or competent authorities of the Member States, the applicant shall submit the application for making amendments to the master file of a pandemic preparedness vaccine (pandemic strain update) to the competent authority (expert organisation) of the reference state in accordance with paragraph 4.1.3 of Appendix No. 19 to the Rules to include the pandemic strain in the pandemic preparedness vaccine (pandemic strain update).

3.2. Requirements for the master file of a pandemic preparedness vaccine in the event of a pandemic threat

In the event of a pandemic threat, the master file of a pandemic preparedness vaccine shall contain the data on the potential pandemic strain(s) (data requirements are given in Section 5 of these Requirements). The applicant shall have the right to submit the master file containing the data on a new strain(s) in a vaccine and compiled on the basis of the available data in order to establish post-authorisation measures (authorisation as a pandemic preparedness vaccine) on the conditions that in the event of a pandemic threat and after a pandemic is duly recognised by the WHO, the applicant shall guarantee the submission of the clinical study results to the competent authority (expert organisation) of the reference state and the fulfilment of the requirements in accordance with Section VII of the Rules. After a pandemic threat duly recognised by the WHO, the applicant shall initiate discussions with competent authorities with the competent authorities of the Member States as early as possible.

3.3. Requirements for the application to change the composition of pandemic influenza vaccines (update of a pandemic strain) during a pandemic

After the official recognition of a pandemic (pandemic duly recognised by the WHO according to the established procedure or an epidemic caused by a pandemic influenza type duly recognised by the corresponding competent authorities of the Member States), the applicant shall have the right to submit the application to change the composition of pandemic influenza vaccines (update of a pandemic strain) to the competent authority (expert organisation) of the reference state in order to include the declared pandemic strain in the pandemic vaccine (update of the pandemic strain).

In the absence of certain non-clinical or clinical data regarding the declared pandemic strain, the applicant shall submit the missing non-clinical and clinical data to the competent authority (expert organisation) of the reference state within the time limit agreed between the applicant and the competent authority (expert organisation) of the reference state.

4. Authorisation of vaccines during a pandemic

4.1. Emergency procedure

After a pandemic duly recognised by the WHO or an epidemic caused by a pandemic influenza type recognised by the corresponding competent authorities of the Member States, the authorisation of a new pandemic vaccine is carried out using the emergency procedure.

In the absence of a pandemic, the applicant shall have the right to submit the master file containing incomplete data to the competent authority (expert organisation) of the reference state in order to

authorise a new pandemic vaccine on the condition that, once the WHO declares a pandemic, the applicant will supply the missing clinical data to the competent authority (expert organisation) of the reference state and fulfil the requirements for the authorisation of vaccines with the establishment of post-authorisation measures (conditional approval) in accordance with Section VII of the Rules. The applicant shall include the appropriate rationale of the possibility of establishing post-authorisation measures, description of the missing data in the master file and attach to it a written obligation to submit these data to the competent authority (expert organisation) of the reference state by amending the master file of influenza vaccines. The applicant shall initiate discussions with competent authorities with the competent authorities of the Member States as early as possible.

4.2. Authorisation of a seasonal or pre-pandemic vaccine as a pandemic influenza vaccine

Depending on the pandemic development situation, epidemiologic situation and (or) where no pandemic preparedness vaccine is already authorised, it is allowed to change the strain composition of the corresponding seasonal or pre-pandemic vaccine in accordance with paragraph 4.1.3 of Appendix No. 19 to the Rules on the conditions that the introduction of these changes will ensure the quality, safety and effectiveness of an influenza vaccine and is feasible from a scientific perspective.

If it becomes necessary to authorise a seasonal or pre-pandemic influenza vaccine as a pandemic influenza vaccine, the applicant shall initiate discussions with competent authorities with the competent authorities (expert organisations) of the Member States as early as possible in order to agree upon the content of the master file of a seasonal or pre-pandemic influenza vaccine.

5. Procedure for modification of the strain composition of seasonal influenza vaccines

5.1. General requirements for the procedure for modification of the strain composition of seasonal influenza vaccines

The application and the master file of seasonal influenza vaccines shall comply with the requirements established in Appendix No. 1 to the Rules and shall be submitted in the format of the Common Technical Document (hereinafter referred to as the CTD).

It is allowed to submit the master file of a seasonal influenza vaccine which includes only relevant sections of the CTD corresponding to the amendments made and the nature of which is determined by the change (update) in the strain composition. The absence of some of the CTD section or submission of the incomplete CTD requires a justification (with stating the reasons for the absence of such sections and (or) for submission of an incomplete document).

The requirements for the modules of the master file of seasonal influenza vaccines established in Subsections 5.2 - 5.5 of these Requirements are provided with the section numbers of the CTD in accordance with the structure of the master file under Appendix No. 4 to the Rules.

5.2. The requirements for the documents of the master file of a seasonal inactivated influenza vaccine when making changes to the strain composition of seasonal inactivated influenza vaccines

The application to change the strain composition of seasonal inactivated influenza vaccines shall be submitted together with the master file containing the sections specified below. Any deviation from the requirements (including the absence of the necessary or additional data) should be justified in the relevant section of Module 3 of the master file and in the appropriate summary (overview) of Module 2 of the master file and should be discussed with the competent authorities (expert organisations) of the reference state before the submission of the application to the competent authority (expert organisation) of the reference state.

Module 1. Administrative Information

1. Cover letter (electronic submission of the documents in the format of the CTD (hereinafter referred to as the eCTD))

1.1. Table of contents (not required if submitted in eCTD format)

1.2. General documentation

1.2.1. Variation application

1.2.2. Documents confirming the payment for expert work and (or) payment of the authorisation fee (charge) according to the legislation of the authorising Member State

1.3. Summary of product characteristics, instruction for medical use (package leaflet), labelling

1.3.1. Drafts of summary of product characteristics, instruction for medical use (package leaflet), labelling layouts, made in accordance with the requirements for the instruction for medical use of drug products and summary of characteristics of drug products for human use, approved by Decision of the Council of the Eurasian Economic Commission No. 88 dated November 3, 2016 (hereinafter referred to as the Requirements for the instruction for medical use of drug products)

Only changes related to the strains used for the epidemic season may be introduced in these texts.

1.7. Information about the experts

1.7.1. Information about the expert preparing the quality summary

Module 2. CTD Summary

2.1. Content of Modules 2 - 5

Content of Modules 2 - 5 (not required if submitted in eCTD format)

2.2. CTD Introduction

Update or addendum to the previous Introduction (if appropriate).

2.3. Quality Overall Summary

Update or addendum to previous Quality Overall Summary.

Module 3. Quality

3.2.S. Active drug substance (hereinafter referred to as an ADS)

3.2.S.2. ADS manufacture

3.2.S.2.3. Control of source materials

Should include:

seed lots: history, derivation procedure (source, date, conditions), strain passport;

passage history (passage number, passage conditions, cultivation substrate);

characterisation of haemagglutinin and neuraminidase (data of serologic tests and (or) molecular genetic testing methods)

test protocols (including test results on seed lots).

3.2.S.2.4. Control of critical steps and intermediates

3.2.S.2.5. Manufacturing process validation and/or evaluation

Manufacturing process validation for monovalent bulks (intermediate monovalent vaccine) should

include:

manufacturing process strain specific changes;

validation of critical manufacturing steps associated with new strains;

virus inactivation process;

virus splitting efficiency (if applicable).

3.2.S.3. Description of ADS characteristics

Selection of characterisation studies (particle size distribution, presence of aggregates, etc.)

3.2.S.4. Quality control of ADS (monovalent vaccines)

3.2.S.4.1. Specification

Copies of approved specifications in a tabular format.

3.2.S.4.2. Analytical procedures

3.2.S.4.3. Validation of analytical procedures

Validation of a single radial immunodiffusion test for a new strain(s) taking into account relevant reference standards.

3.2.S.4.4. Batch analysis (batch analysis results)

should include the following test results of the first three batches of monovalent bulks (including identification parameters test of haemagglutinin and neuraminidase) on the conditions that these products are from:

each working seed lot of a new master seed lot of a new strain(s);

each working seed lot from previously approved master seed lot of a new strain(s) (if the procedure of working seed lot preparation is different from the procedure of working seed lot preparation approved earlier).

3.2.S.7. Stability

Stability tests on the ADS: it is necessary to provide results from monovalent bulks where they are used for more than one year.

3.2.P. Drug product

3.2.P.1. Description and composition of the drug product

The composition of the vaccine should be provided.

3.2.P.2. Pharmaceutical development

3.2.P.2.2.1. Pharmaceutical form development

Reformulated vaccine (new epidemic season’s strains) and, if a clinical trial has been requested to support the annual update, the Certificate of Analysis of the batch used in the clinical trial when the specified certificate is available.

3.2.P.3. Manufacturing process of the drug product

3.2.P.3.2. Batch formula (manufacturing formula)

3.2.P.5. Quality control of the drug product

3.2.P.5.1. Specifications

Copies of approved specifications and specification parameter determination methods in a tabular format.

3.2.P.5.3. Validation of analytical procedures

Validation of a single radial immunodiffusion test for a new strain(s) (either using trivalent bulk or drug product)

3.2.P.8. Stability of the drug product:

stability data from previous season;

commitment to investigate the stability of the vaccine during the period of its use;

post-authorisation stability protocol for the vaccine.

If the seed lot is tested for extraneous agents using the polymerase chain reaction (hereinafter referred to as the PCR), and if further to discussion with the expert organisation of the reference state the need for additional PCR testing of the seed lot has been agreed, these data should be included in the master file of influenza vaccines.

5.3. Requirements for submission of additional data (after the request of the competent authority of the Member State)

Upon the request of the additional data (depending on the type of the additional data submitted), relevant sections of the master file should be submitted for the introduction of changes in the format of the CTD.

Module 1. Administrative Information

1. Cover letter (like in the CTD)

1.1. Table of contents (not required if submitted in eCTD format)

1.7. Information about the experts

1.7.1. Information (brief overview) about the expert preparing the quality summary

Module 2. CTD Summary

2.1. Content of Modules 2 - 5 (not required if submitted in eCTD format)

2.2. CTD Introduction

Update or addendum to the previous Introduction (if appropriate).

2.3. Quality Overall Summary

Update or addendum to previous Quality Overall Summary (if applicable).

2.5. Clinical data overview

Update or addendum to the previous overview (if appropriate).

2.7. Clinical data summary

Update or addendum to the previous clinical overview (if appropriate).

Information contained in Modules 3 - 5 should be submitted in case of the request of the additional quality data, non-clinical <1> and (or) clinical <2> data.

5.4. Requirements for the master file documents to change the strain composition of live attenuated influenza vaccines

The application to change the strain composition of live attenuated influenza vaccines should contain the documentation specified below. Deviation from the requirements (absence of the necessary or additional data) should be justified in the relevant section of Module 3 and in the appropriate summary (overview) and should be discussed with the competent authorities of the Member States before the submission of the application.

Module 1. Administrative Information

1. Cover letter (like in the CTD)

1.1. Table of contents (not required if submitted in eCTD format)

1.2. General documentation

1.2.1. Variation application

1.2.2. Documents confirming the payment of the fee (charges) for confirmation of marketing authorisation (re-registration) and expertise in cases stipulated in the legislation of the reference Member State

1.3. Summary of product characteristics, instruction for medical use (package leaflet), labelling

1.3.1. Drafts of summary of product characteristics, instruction for medical use (package leaflet), labelling layouts, made in accordance with the requirements for the instruction for medical use of drug products

Only changes related to the strains used for the epidemic season may be introduced in these texts.

1.7. Information about the experts

1.7.1. Information (brief overview) about the expert preparing the quality summary

Module 2. CTD Summary

2.1. Content of Modules 2 - 5 (not required if submitted in eCTD format)

2.2. CTD Introduction

Update or addendum to previous CTD Introduction (if appropriate).

2.3. Quality Overall Summary

Update or addendum to previous Quality Overall Summary.

Module 3. Quality

3.2.S.2. ADS manufacture

3.2.S.2.3. Control of source materials

Seed lot batches (production history of the seed lot) including:

description of the derivation of the seed lot starting from master attenuated donor seed lot and WHO recommended strain(s);

history of cold-adapted reassortant strain derivation using a WHO recommended strain (indicating the place of extraction and passage history) and the attenuated donor used.

study of the genotype of the attenuated strain. Results of attenuated strain sequencing;

phenotypic characterisation: temperature-sensitive (thermolabile) phenotype (ts) and cold-adapted phenotype (ca), including phenotype based on the attenuation test results;

genetic stability for the seed lot including relevant genotypic and phenotypic markers (e.g. full genetic sequencing);

analytical protocols (including extraneous agents safety test and infectious diseases activity data) <3>;

neurovirulence tests <4>.

3.2.S.2.4. Control of critical steps and intermediates

3.2.S.2.5. Manufacturing process validation and/or evaluation

For the manufacturing process of the monovalent bulks (for manufacturing process strain specific changes).

3.2.S.4. Quality control of the ADS

3.2.S.4.1. Specification

Copies of approved specifications in a tabular format.

3.2.S.4.2. Analytical procedures

3.2.S.4.3. Validation of analytical procedures

Validation of analytical procedures linked to a new strain(s) and the use of new reagents.

3.2.S.4.4. Batch analysis (batch analysis results)

Results of the first three batches of monovalent bulks.

3.2.S.7. Stability

Stability tests on the ADS: results from monovalent bulks where they are used for more than one year.

3.2.P. Drug product

3.2.P.1. Description and composition of the drug product

Composition of the drug product.

3.2.P.2. Pharmaceutical development

3.2.P.2.2.1. Pharmaceutical form development

Reformulated vaccine (new epidemic season’s strains) and, if a clinical trial has been requested to

support the annual update, the Certificate of Analysis of the batch used in the clinical trial when available.

3.2.P.3. Manufacturing process of the drug product

3.2.P.3.2. Batch formula (manufacturing formula)

3.2.P.5. Quality control of the drug product

3.2.P.5.1. Specifications

Copies of approved specifications and specification parameter determination methods in a tabular format.

3.2.P.5. Quality control of the drug product

3.2.P.5.3. Validation of analytical procedures

Validation of analytical procedures (using trivalent bulks or finished drug product).

3.2.P.5.4. Batch analysis results

3.2.P.6. Reference standards and materials

Reference standards and materials for a new strain(s)

3.2.P.8. Stability of the drug product:

stability data from previous season;

stability study obligations;

post-authorisation stability protocol for the vaccine.

5.5. Requirements for submission of additional data upon the request of the competent authorities (expert organisations) of the Member States

Upon the request of the additional data depending on the type of the additional data submitted, relevant sections of the master file should be submitted for the introduction of changes in the format of the CTD.

Module 1. Administrative Information

1. Cover letter (like in the CTD)

1.1. Table of contents (not required if submitted in eCTD format)

1.7. Information about the experts

1.7.1. Information (brief overview) about the expert preparing the quality summary

Module 2. CTD Summary

2.1. Content of Modules 2 - 5 (not required if submitted in eCTD format)

2.2. CTD Introduction

Update or addendum to previous CTD Introduction (if appropriate).

2.3. Quality Overall Summary

Update or addendum to previous Quality Overall Summary (if applicable).

2.5. Clinical data overview

Update or addendum to the previous clinical overview (if appropriate).

Information contained in Modules 3 - 5 should be submitted in case of the request of the additional quality data, non-clinical <1> and (or) clinical <2> data.

<1> In principle, there is no need to provide non-clinical and (or) clinical data to support seasonal influenza strain updates.

<2> The reactogenicity and immunogenecity profiles of the vaccine should be monitored by means of safety surveillance and product-specific effectiveness studies.

<3> If the seed lot is tested for extraneous agents using the PCR, and if further to discussion with the expert organisation the need for additional PCR testing of the seed lot (master and (or) working seed lot) has been agreed, these data should be included in the master file.

<4> Neurovirulence testing of annual updates (i.e. antigenically drifted strains) is normally not required. Neurovirulence testing will be required if a new HA subtype of influenza A virus or a novel influenza B virus type differing from the currently circulating genetic lineages is included in the vaccine or in case specific safety concerns arise.