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 ($\geq$ 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.