ANNEX

to Decision No.
of the Eurasian Economic Commission
dated , 20

AMENDMENTS
to the Rules of Marketing Authorization and Assessment of Medicinal Products for Human Use

1. Paragraph 19 shall be supplemented after the 20th indent by the following indent:

"confidential data" means personal data and data which is not publicly available and whose disclosure may have negative consequences for the economic interest and competitive position of the owner of such data. Confidential data includes, but is not limited to, a detailed description of the manufacturing process, specification data, the strategy of the applicant or marketing authorization holder for further marketing authorization actions in relation to the medicinal product in question, information regarding comments received during and as a result of pharmaceutical manufacturing site inspections and other pharmaceutical inspections, as well as names and locations of quality control manufacturing sites;".

2. Paragraph 47 shall be supplemented after the second indent by the following indent:

"written confirmation from the applicant of the intention to approve the draft final assessment report for ensuring the confidentiality of information contained in the marketing authorization application for the medicinal product (if there is such an intention);".

3. Paragraph 60 shall be supplemented by the following indents:

"If the marketing authorization application contains the applicant's documented intention to approve the final assessment report, the authorized

authority (expert organization) of the reference Member State shall send to the applicant the draft final assessment report for ensuring the confidentiality of information contained in the marketing authorization application for the medicinal product before publishing the final assessment report in the Common Register. The draft final assessment report shall be transmitted to the applicant in electronic form and shall be deemed received after one business day from the date of its sending.

The applicant shall be given no more than 10 business days from the date of receipt of the draft final assessment report (which shall not be included in the period of marketing authorization and assessment of the medicinal product) to approve the above draft and provide the justification for the exclusion of the confidential data, including commercial secrets. The applicant shall be entitled to mark confidential information not to be published by highlighting it with tracked changes in the draft final assessment report intended for subsequent publication in the Common Register and send it to the authorized authority (expert organization) of the reference Member State in electronic form.

The applicant's response shall be assessed within a period not exceeding five business days from the date of receipt of the applicant's response which shall not be included in the period of marketing authorization and assessment of the medicinal product.

On the basis of the assessment, the authorized authority (expert organization) shall be entitled to accept the exclusion of information, as proposed by the applicant. In this case, if the authorized authority of the reference Member State makes a positive decision on the marketing authorization of the medicinal product, the authorized authority of the reference Member State shall make publicly available in the Common Register the final assessment report as laid down in Appendix 16 hereto excluding the confidential data. If the applicant fails to provide the above information within the fixed time, the final assessment report shall be deemed approved by the applicant."

4. In subparagraph b of paragraph 63, as well as paragraphs 76, 81, 111, and 180, the words “Risk Management Plan” shall be replaced with the words “summary of the Risk Management Plan”.

5. Paragraph 86 shall be supplemented after the second indent by the following indent:

“written confirmation from the applicant of the intention to approve the draft final assessment report for ensuring the confidentiality of information contained in the marketing authorization application for the medicinal product (if there is such an intention);”.

6. Paragraph 105 shall be supplemented by the following indents:

“If the marketing authorization application contains the applicant’s documented intention to approve the final assessment report, the applicant shall be given no more than 10 business days from the date of receipt of the final assessment report (which shall not be included in the period of marketing authorization and assessment of the medicinal product) to approve the final assessment report for ensuring the confidentiality of information contained in the marketing authorization application for the medicinal product and provide the justification for the exclusion of the confidential data, including commercial secrets.

The applicant shall be entitled to mark confidential information not to be published by highlighting it with tracked changes in the draft final assessment report intended for subsequent publication in the Common Register and send it to the authorized authority (expert organization) in electronic form.

The applicant’s response shall be assessed within a period not exceeding five business days from the date of receipt of the applicant’s response which shall not be included in the period of marketing authorization and assessment of the medicinal product.

On the basis of the assessment, the authorized authority (expert organization) shall be entitled to accept the exclusion of information, as proposed by the applicant. In this case, if the authorized authority of the reference Member

State makes a positive decision on the marketing authorization of the medicinal product, the authorized authority of the reference Member State shall make publicly available in the Common Register the final assessment report as laid down in Appendix 16 hereto excluding the confidential data. If the applicant fails to provide the above information within the fixed time, the final assessment report shall be deemed approved by the applicant.”

7. Paragraph 152 shall be supplemented by the following indent:

“When the authorized authority (expert organization) of the reference Member State updates the assessment report after making amendments to the marketing authorization application, the confidential data previously agreed with the applicant shall be excluded as well. If amendments made to the marketing authorization application affect sections of the assessment report that require the exclusion of confidential data, such data shall be excluded in accordance with the procedure and terms of interaction with the applicant, as specified in paragraphs 60 and 105 hereof.”

8. Paragraph 1.10.3 of Appendix 1 to the above Rules shall be supplemented after the words “Risk Management Plan” by the words “and the summary of the Risk Management Plan”.

9. Paragraph 1.10.3 of Appendix 4 to the above Rules shall be supplemented after the words “Risk Management Plan” by the words “and the summary of the Risk Management Plan”.

10. In Appendix 19 to the above Rules:

a) in Annex V:

the Annex shall read as follows:

“Annex V

Classification of variations to the marketing authorization application for a medicinal product

Variations to the marketing authorization application 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 (PMFs) and Vaccine Antigen Master Files (VAMFs).

Where reference has to be made to specific variations in this Annex, the variation in question shall 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 to this Appendix. It is also indicated which minor variations of Type IA require immediate notification as established in paragraphs 2.1.1 and 3.1.1 of this Appendix;

A list of variations that should be considered as minor variations of Type IB. In accordance with paragraph 1.3 of this Appendix, this category shall be assigned by default. Accordingly, this Annex is not intended to establish an exhaustive list for this category of variations.

This Annex does not deal with the classification of extensions as they are exhaustively listed in Annex I to this Appendix. All changes specified in Annex I to this Appendix must be considered extensions of the marketing authorizations.

Any other change cannot be considered as an extension of the marketing authorization.

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 Appendix, 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 authorized 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 process the change as a Type II variation and send a request to the applicant to upgrade the application and submit documents necessary for this change. Subsequent consideration of the upgraded application shall be carried out within the time limits established for a Type II variation from the date of receipt of the response to the request.

"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 an analytical procedure and acceptance criteria are set, e.g. assay, identity, water content. The addition or deletion of a specification parameter therefore includes its corresponding analytical procedure and acceptance criteria.

"Product information" refers to the summary of product characteristics, the patient leaflet (package leaflet), packaging mock-ups, and the normative document of a medicinal product.

"Manufacturing license" refers to a license or any other authorization for manufacturing issued in the manner established by the legislation of the manufacturing country.

Specific supporting data for Type IB and Type II variations will depend on the specific nature of the change.

There is no need to notify the Member States' authorized 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 marketing authorization application for an authorized medicinal product. Applicants are reminded that compliance with the updated monograph should be implemented within 180 calendar days.

Therefore, Section D of this Annex provides a list of variations which are specific to such PMFs or VAMFs. Following assessment of these variations, any marketing authorization application containing references to these PMFs or VAMFs must be updated in accordance with Subsection 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 application should also be assessed in accordance with this Annex.

References in this Annex to changes to the marketing authorization application mean addition, replacement, or deletion, unless specifically indicated. If amendments to the marketing authorization application only concern editorial changes (correction of technical errors and typos), such changes shall be considered by authorized authorities (expert organizations) as editorial changes if there are detailed explanations in the Cover Letter (Section 1.0 of the Common Technical Document) or as undeclared changes and therefore inaccurate information in the contrary case.

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 marketing authorization application has not been changed by the editorial changes beyond the scope of the variation submitted should be provided in the Cover Letter (Section 1.0 of the Common Technical Document). 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.";

in section A of the table:

Subsections A.1–A.7 shall read as follows:

“A. Administrative changes

A.1. Change of marketing authorization holder	Conditions to be fulfilled	Documents and data	Procedure
a) Change of name and/or address of the marketing authorization holder	1	1, 3	IA_{IN}
b) Transfer of marketing authorization certificate from one marketing authorization holder to another juridical person	2	1, 2, 3, 4	IA_{IN}
Conditions 1. The marketing authorization holder must remain the same juridical person. 2. The marketing authorization holder is another juridical person.			
Documentation 1. A copy of the document issued by the relevant authorized authority of the country of registration of the juridical person being the marketing authorization holder (e.g. a tax authority) that specifies the name and/or address of the new marketing authorization holder or the new name and/or address of the marketing authorization holder. 2. Documents justifying the transfer of the marketing authorization certificate(s) and confirming the ability of the new marketing authorization holder to ensure the proper performance of all the marketing authorization holder’s obligations; copy of the document confirming the transfer of the marketing authorization certificate from one juridical person to another; revised pharmacovigilance summary or revised pharmacovigilance system master file, if included in the marketing authorization application; information about the organization responsible for handling complaints in the Eurasian Economic Union. 3. Medicinal product information revised in the relevant sections. 4. Document(s) submitted by the juridical person to which the powers of the marketing authorization holder are transferred, confirming the absence of changes in medicinal product information that are not related to the transfer of the marketing authorization.			
A.2. Change in the (brand) name of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) medicinal products authorized in accordance with the Rules of Marketing Authorization and Assessment	1	1, 2	IAIN
b) medicinal products authorized only in the reference Member State,	–	1, 2	IB

including in accordance with the legislation of the Member State			
Conditions 1. The check by the authorized authority (expert organization) of the reference Member State on the acceptability of the new (brand) name has been finalized and was positive.			
Documentation 1. Justification of the applicant for the acceptability of the new (brand) name. 2. Revised medicinal product information.			
A.3. Change in name of the active pharmaceutical ingredient or of an excipient	Conditions to be fulfilled	Documents and data	Procedure
	1	1, 2	IA_{IN}
Conditions 1. The active pharmaceutical ingredient/excipient must remain the same.			
Documentation 1. Justification for the WHO to change the name of the active pharmaceutical ingredient. For an excipient: justification for amending the Union's directory (classifier) of excipients. Proof that the change is in line with the Pharmacopoeia of the Union (if applicable) or otherwise with a Pharmacopoeia of a Member State. A declaration that the name of the herbal medicinal product is in accordance with the acts of the Union's governing bodies in the field of medicines circulation. 2. Revised medicinal product information.			
A.4. Change in the name and/or address of: a manufacturer (including, where relevant, quality control testing sites); or an APIMF holder; or a supplier of the active pharmaceutical ingredient, starting material, reagent, or intermediate used in the manufacture of the active pharmaceutical ingredient (where specified in the marketing authorization application) where no Ph. Eur. Certificate of Suitability is part of the approved marketing authorization application; or a manufacturer of a novel excipient (where specified in the marketing authorization application)	Conditions to be fulfilled	Documents and data	Procedure
	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 authorized authority (e.g. a tax authority) in which the new name and/or address is mentioned. 2. Amendment of the relevant section(s) of the marketing authorization application. 3. In case of change in the name of the active pharmaceutical ingredient master file (APIMF) holder, updated letter of access.			
A.5. Change in the name and/or address of a manufacturer/importer of the medicinal product (including batch release or quality control testing sites)	Conditions to be fulfilled	Documents and data	Procedure
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 manufacturing license, if available; or a formal document from a relevant authorized authority (e.g. a tax authority) in which the new name and/or address is mentioned. 2. If applicable, amendment of the relevant section(s) of the marketing authorization application, including revised medicinal product information as appropriate.			
A.6. Change in ATC Code	Conditions to be fulfilled	Documents and data	Procedure
a) Change following approval of or amendment to ATC Code by the WHO	1	1	IA
b) Change at the applicant's initiative of a code other than the code assigned by the WHO	–	1	IB
Conditions 1. Change following approval of or amendment to ATC Code by the WHO.			
Documentation 1. Revised medicinal product information.			

A.7. Deletion of manufacturing sites for an active pharmaceutical ingredient, intermediate or medicinal product, a packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the marketing authorization application)	Conditions to be fulfilled	Documents and data	Procedure
	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. 2. The deletion should not be due to critical deficiencies concerning manufacturing.			
Documentation 1. The paragraph of the variation application form on changes should clearly outline the previously approved and proposed manufacturers as listed in Section 2 of the application form. 2. Amendment of the relevant section(s) of the marketing authorization application, including revised medicinal product information as appropriate.			

”;

Subsection A.8 shall be invalidated;

the following Subsections A.9–A.11 shall be added:

“

A.9. Changes to correct typos and errors in marketing authorization application documents	Conditions to be fulfilled	Documents and data	Procedure
a) changes affecting medicinal product information	1	1, 2	IA_{IN}
b) changes not affecting medicinal product information	1	1, 2	IB
Conditions 1. Errors or typos are technical in nature and do not affect the quality, safety, or efficacy of the medicinal product.			
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application, including revised medicinal product information as appropriate, as well as document with tracked changes. 2. Justification of the technical nature of the identified error or typo.			

A.10. Change in the name, organizational and legal form, or address of the authorized authority or organization carrying out assessment and marketing authorization of medicinal products	Conditions to be fulfilled	Documents and data	Procedure
	–	1	IA
Documentation 1. Revised medicinal product information.			
A.11. Change in the name of the primary packaging material of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
	1	1, 2, 3	IA
Conditions 1. The material of the packaging (closure) system remains the same.			
Documentation 1. Copy of or link to a regulatory document on approval or change of materials. If applicable, proof that the change is in line with the Pharmacopoeia of the Union or otherwise with a Pharmacopoeia of a Member State. 2. A declaration that the name of the material is in accordance with the acts of the Union's governing bodies. 3. Revised medicinal product information.			

”;

c) Section B of the table shall read as follows:

“B. Quality changes

B.I. Active pharmaceutical ingredient

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 pharmaceutical ingredient or change in the active pharmaceutical ingredient manufacturer (including, where relevant, quality control testing sites), where no Ph. Eur. Certificate of Suitability is	Conditions to be fulfilled	Documents and data	Procedure

part of the approved marketing authorization application			
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, 9	IA_{IN}
b) Introduction of a manufacturer of the active pharmaceutical ingredient supported by an APIMF <*>	–	–	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 pharmaceutical ingredient, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting bioavailability <*>	–	–	II
d) New manufacturer of material for which an assessment is required of viral safety and/or transmissible spongiform encephalopathy (TSE) risk	–	–	II
e) The change relates to a biological active pharmaceutical ingredient or a starting material/reagent/intermediate used in the manufacture of a biological medicinal product	–	–	II
f) Changes to quality control testing arrangements for the active pharmaceutical ingredient – 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 pharmaceutical ingredient that is not supported by an APIMF and requires significant update to Section 3.2.S of the marketing authorization application for the medicinal product <*>	–	–	II
h) Addition of an alternative sterilization site for the active pharmaceutical ingredient using a method of the Pharmacopoeia of the Union or otherwise the methods of other pharmacopoeias in accordance with the Concept for Harmonizing the Pharmacopoeias of the Eurasian Economic Union Member States approved by Decision No. 119 of the Eurasian Economic Commission's Board dated September 22, 2015 (hereinafter referred to as the Concept)	–	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 Bank	–	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 pharmaceutical ingredients, the specifications (including in-process controls, methods of analysis of all materials), method of preparation (including the batch size) and detailed route of synthesis are identical to those already approved.

2. The active pharmaceutical ingredient is not a biological substance or sterile.
3. Materials of human or animal origin are used in the process and the active pharmaceutical ingredient manufacturer:
   does not use any new supplier for which assessment is required of viral safety or of compliance with the Pharmacopoeia of the Union and Chapter 24 of the Rules of Biological Medicinal Products Research on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products;
   uses a new supplier for which such assessment has been performed.
4. Method transfer from the old to the new site has been successfully completed.
5. The particle size specification of the active pharmaceutical ingredient and the corresponding analytical method remain the same.

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application, if applicable.
2. Proof from the marketing authorization holder or the APIMF 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 preparation and manufacturing route) quality control procedures and specifications of the active pharmaceutical ingredient and of the starting material/reagent/intermediate in the manufacturing process of the active pharmaceutical ingredient (if applicable) are the same as those already approved.
3. 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 authorized authority and shown to comply with the Pharmacopoeia of the Union and Chapter 24 of the Rules of Biological Medicinal Products Research on minimizing the risk of transmitting the animal spongiform encephalopathy agents via human and veterinary medicinal products. Such documentary evidence should include the following information: name of manufacturer, animal species and tissues from which the material is a derivative; country of origin of the material, its previous use and acceptance.
4. Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the active pharmaceutical ingredient from the current and proposed manufacturers/sites.
5. The variation application form should clearly outline the previously approved and proposed manufacturers as listed in Section 2.5 of the application form.
6. A declaration by the qualified person of each of the manufacturing authorization holders listed in the application where the active pharmaceutical ingredient is used as a starting material or a declaration by the qualified person of each of the manufacturing authorization holders listed in the application as those carrying out the batch release stage. These

declarations should state that the active pharmaceutical ingredient manufacturer referred to in the application carries out its activities in accordance with the Rules of Good Manufacturing Practice. A single declaration may be acceptable under certain circumstances — see the note under variation B.II.b.1. 7. Where relevant, a commitment of the active pharmaceutical ingredient manufacturer to inform the marketing authorization holder of any changes to the manufacturing process, specifications, and analytical procedures of the active pharmaceutical ingredient. 8. Proof that the proposed site is appropriately authorized for the manufacturing operation concerned. 9. Documents confirming that the active pharmaceutical ingredient manufacturer is part of the same pharmaceutical group (e.g. a letter of confirmation).			
Note: <*>	In appropriate cases, it is also necessary to submit comparative dissolution profile data for the medicinal product with the active pharmaceutical ingredient produced at the previous site and two batches of the medicinal product with the active pharmaceutical ingredient produced at the new manufacturing site.		
B.I.a.2. Changes in the manufacturing process of the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
a) Minor change in the manufacturing process of the active pharmaceutical ingredient	1, 2, 3, 4, 5, 6, 7	1, 2, 3	IA
b) Substantial change to the manufacturing process of the active pharmaceutical ingredient which may have a significant impact on the quality, safety, or efficacy of a medicinal product	–	–	II
c) The change refers to a biological substance or use of a different chemically derived substance in the manufacture of a biological substance, which may have a significant impact on the quality, safety, and efficacy of the medicinal product and is not related to a	–	–	II

post-approval change management protocol			
d) The change relates to a herbal medicinal product and there is a change to any of the following: geographical source of herbal substances, manufacturing route, or production	–	–	II
e) Minor change to the Restricted Part of the APIMF	–	1, 2, 3, 4	IB

Conditions

1. No adverse change in the qualitative and quantitative impurity profile or in physico-chemical 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 pharmaceutical ingredient or intermediates are unchanged.
4. The change is fully described in the open part (Applicant's Part) of the APIMF (if applicable).
5. The active pharmaceutical ingredient is not a biological substance.
6. The change does not refer to the geographical source of herbal substances, manufacturing route, or production of a herbal medicinal product.
7. The change does not refer to the Restricted Part of the APIMF.

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application, 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. Copies of approved specifications of the active pharmaceutical ingredient (in the form of a link to the relevant document in the marketing authorization application sequence or an annex to the cover letter).
4. Proof from the marketing authorization holder or the APIMF holder, where applicable, that there is no change in the qualitative and quantitative impurity profile or in physico-chemical properties, that the synthetic route remains the same and that the specifications of the active pharmaceutical ingredient or intermediates are unchanged.

Note	Substantial changes in active pharmaceutical ingredients obtained by chemical synthesis refer to changes to the synthetic route or manufacturing conditions which may have a potential to

	change important quality characteristics of the active pharmaceutical ingredients, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting bioavailability.

B.I.a.3. Change in batch size (including batch size ranges) of the active pharmaceutical ingredient or intermediate used in the manufacturing process of the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
a) Up to 10-fold increase compared to the originally approved batch size	1, 2, 3, 4, 5, 6, 7, 8	1, 2, 5	IA
b) Up to 10-fold decrease compared to the originally approved batch size	1, 2, 3, 4, 5	1, 2, 5	IA
c) The change requires assessment of the comparability of a biological active pharmaceutical ingredient	–	–	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 active pharmaceutical ingredient is increased/decreased without process change (e.g. duplication of line)	–	1, 2, 3, 4	IB

Conditions

1. Any changes to the manufacturing methods affect only processes necessitated by batch size 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 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 pharmaceutical ingredient/intermediates remain the same.

7. The active pharmaceutical ingredient is not sterile.
8. The batch size is within the 10-fold range of the batch size provided for 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 marketing authorization application.
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 pharmaceutical ingredient 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 actions).
4. Copies of approved specifications of the active pharmaceutical ingredient (and of the intermediate, if applicable) (in the form of a link to the relevant document in the dossier sequence or an annex to the cover letter).
5. A declaration from the marketing authorization holder or the APIMF 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 pharmaceutical ingredient/intermediates remain the same.

B.I.a.4. Change to in-process tests or acceptance criteria applied during the manufacture of the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
a) Tightening of in-process acceptance criteria	1, 2, 3, 4	1, 2	IA
b) Addition of a new in-process test or acceptance criteria	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 acceptance criteria, which may have a significant effect on the overall quality of the active pharmaceutical ingredient	–	–	II

e) Deletion of an in-process test which may have a significant effect on the overall quality of the active pharmaceutical ingredient	–	–	II
f) Addition or replacement of an in-process test for safety or quality reasons	–	1, 2, 3, 4, 6	IB
g) Minor change to the analytical procedure of in-process control	8, 9, 10, 11	1, 7, 8	IA

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification acceptance criteria (e.g. made during the procedure for marketing authorization 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 acceptance criteria.
4. The analytical procedure remains the same, or changes in the analytical procedure are minor.
5. No new test method concerns 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 pharmaceutical ingredient (except for 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 pharmaceutical ingredient), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any change in the frequency of testing.
8. Appropriate validation studies have been performed in accordance with the acts of the Union's governing bodies in the field of medicines circulation and show that the updated analytical procedure is at least equivalent to the former analytical procedure.
9. The limits of the total impurities are not changed, and no new unqualified impurities are detected.
10. The method of analysis remains the same, and changes in the analytical procedure are minor (e.g. a change in column length or temperature, but not a different type of column).
11. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active pharmaceutical ingredient (except for standard pharmacopoeial microbiological methods).

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application. 2. Comparative table of current and proposed in-process tests. 3. Details of any new non-pharmacopoeial analytical procedure and validation data, where relevant. 4. Batch analysis data on two production batches (three production batches for biologicals, unless otherwise justified) of the active pharmaceutical ingredient for all specification parameters. 5. Justification/risk assessment from the marketing authorization holder or the APIMF holder, as appropriate, that the in-process tests are non-significant, or that the in-process tests are obsolete. 6. Justification from the marketing authorization holder or APIMF holder as appropriate for the new in-process test and limits. 7. Comparative table of changes in the analytical procedure. 8. Details of any new non-pharmacopoeial analytical procedure and validation data (where relevant) confirming that the updated analytical procedure is at least equivalent to the previous one.

B.I.a.5. Changes to the active pharmaceutical ingredient of a seasonal, prepandemic, or pandemic influenza vaccine	Conditions to be fulfilled	Documents and data	Procedure
a) Replacement of the strain(s) in a seasonal, prepandemic, or a pandemic influenza vaccine	–	–	II

B.I.b) Control of the active pharmaceutical ingredient

B.I.b.1. Change in the specification parameters and/or acceptance criteria of an active pharmaceutical ingredient, starting material/intermediate/ reagent used in the manufacturing process of the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
a) Tightening of specification acceptance criteria for biological medicinal products (containing the active pharmaceutical ingredient) subject to batch release by the official control authority of a Member State	1, 2, 3, 4	1, 2	IAIN

b) Tightening of specification acceptance criteria	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, 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 pharmaceutical ingredient and/or the finished product	–	–	II
f) Change outside the approved range of specification acceptance criteria for the active pharmaceutical ingredient	–	–	II
g) Widening of the approved specification acceptance criteria for starting materials/intermediates, which may have a significant effect on the overall quality of the active pharmaceutical ingredient and/or the medicinal product	–	–	II
h) Addition or replacement (excluding a biological substance) of a specification parameter with its corresponding test method for safety or quality reasons	–	1, 2, 3, 4, 5, 7	IB
i) Where there is no monograph for the active pharmaceutical ingredient in the Pharmacopoeia of the Union or another pharmacopoeia according to	–	1, 2, 3, 4, 5, 7	IB

the Concept, a change in specification from in-house to a pharmacopoeia of a third country			
j) Addition or replacement of a specification parameter with its corresponding test method for a biological/immunological active pharmaceutical ingredient	–		II

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification acceptance criteria (e.g. made during the procedure for the marketing authorization of a medicinal product 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 acceptance criteria.
4. The analytical procedure remains the same, or changes in the analytical procedure are minor.
5. Any new test method is based on the general analysis methods described in the Pharmacopoeia of the Union or otherwise on methods described in other pharmacopoeias in accordance with the Concept (e.g., high-performance liquid chromatography (HPLC), spectrophotometry, titrimetry, etc.).
6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active pharmaceutical ingredient (except for standard pharmacopoeial microbiological methods).
7. For any material, the change does not concern a genotoxic impurity. If the change involves the active pharmaceutical ingredient, other than for residual solvents which must be in line with the limits specified in the relevant monograph in the Pharmacopoeia of the Union, any new impurity control should be in line with the Pharmacopoeia of the Union or otherwise any other pharmacopoeia in accordance with the Concept.
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 pharmaceutical ingredient), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any skip of testing.

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical procedure and validation data, where relevant.

4. Batch analysis data on two production batches (three production batches for biologicals, unless otherwise justified) of the relevant substance for all specification parameters. 5. Where appropriate, comparative dissolution profile data for the medicinal product containing the active pharmaceutical ingredient on at least one pilot batch complying with the current and proposed specifications. For herbal medicinal products, comparative disintegration data may be sufficient. 6. Justification/risk assessment from the marketing authorization holder or the APIMF holder, as appropriate, that the in-process parameter is non-significant, or that the in-process parameter is obsolete. 7. Justification from the marketing authorization holder or the APIMF holder, as appropriate, of the new specification parameter and the acceptance criteria.			
B.I.b.2. Change in the analytical procedure for the active pharmaceutical ingredient or the starting material/intermediate/reagent used in the manufacturing process of the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
a) Minor changes to an approved analytical procedure	1, 2, 3, 4	1, 2	IA
b) Deletion of an analytical procedure for the active pharmaceutical ingredient or a starting material/intermediate/reagent, if an alternative analytical procedure is already authorized	7	1	IA
c) Other changes to an analytical procedure (including replacement or addition) for a reagent, which do not have a significant effect on the overall quality of the active pharmaceutical ingredient	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 an analytical procedure (including addition or replacement) for the active pharmaceutical ingredient or a starting material/intermediate	–	1, 2	IB
Conditions 1. Appropriate validation studies have been performed in accordance with the acts of the Union's governing bodies in the field of medicines circulation and show that the updated analytical procedure is at least equivalent to the former analytical procedure. 2. There have been no changes of the total impurity limits; no new unqualified impurities have been detected. 3. The method of analysis remains 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 pharmaceutical ingredient (except for standard pharmacopoeial microbiological methods). 5. Any new test method is based on the general analysis methods described in the Pharmacopoeia of the Union or otherwise in the pharmacopoeia of a Member State or otherwise any other pharmacopoeia according to the Concept (e.g., HPLC, spectrophotometry, titrimetry, etc.). 6. The active pharmaceutical ingredient is not biological. 7. An alternative analytical procedure is already authorized for the specification parameter.			
Documentation 1. Amendment to the relevant section(s) of the marketing authorization application, 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 analytical procedure.			

B.I.c) Container closure system

B.I.c.1. Change in primary packaging of the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
a) Qualitative and/or quantitative composition (change in the composition of the packaging material, change in the packaging material or	1, 2, 3	1, 2, 3, 4, 6	IA

material quality standard)			
b) Qualitative and/or quantitative composition (change in the composition of the packaging material, change in the packaging material or material quality standard) for sterile and non-frozen biological active pharmaceutical ingredients	–	–	II
c) Qualitative and/or quantitative composition (change in the composition of the packaging material, change in the packaging material or material quality standard) for liquid active pharmaceutical ingredients (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 in accordance with the acts of the Union's governing bodies in the field of medicines circulation, and relevant stability parameters have been assessed in at least two pilot scale or industrial batches, and at least three months satisfactory stability data are at the disposal of the applicant at time of implementation. If the proposed packaging is more resistant than the existing packaging, the three months' stability data do not yet have to be available. These studies must be finalized and the data will be provided immediately to the authorized authorities if outside specifications or potentially outside specifications at the end of the shelf-life/retest period (with proposed actions). 3. Sterile, liquid and biological active pharmaceutical ingredients are excluded.			
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application. 2. Appropriate data on the new packaging (e.g. comparative data on permeability, e.g. for O_2, CO_2, moisture, etc.), including a confirmation that the material complies with relevant pharmacopoeial requirements or the acts of the Union's governing bodies on the safety of materials in contact with food products or otherwise with the legislation of the Member States to the extent not regulated by the acts of the Union's governing bodies. 3. Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. there is no migration of components of the proposed material into the content or loss of components of the active pharmaceutical ingredient into the pack), including confirmation			

that the material complies with relevant pharmacopoeial requirements or the acts of the Union's governing bodies on the safety of materials in contact with food products or otherwise with the legislation of the Member States to the extent not regulated by the acts of the Union's governing bodies.

4. A declaration from the marketing authorization holder or the APIMF holder as appropriate that the required stability studies have been started in accordance with the acts of the Union's governing bodies in the field of medicines circulation (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 authorized authorities if outside specifications or potentially outside specifications at the end of the approved shelf life/retest period (with proposed actions).
5. The results of stability studies that have been carried out in accordance with the acts of the Union's governing bodies in the field of medicines circulation, on the relevant stability parameters, on at least two pilot or industrial batches, covering a minimum period of three months, and an assurance that these studies will be finalized, and that data will be provided immediately to the authorized authorities if outside specifications or potentially outside specifications at the end of the approved retest period (with proposed actions).
6. Comparison of current and proposed primary packaging specifications, if applicable.

B.I.c.2. Change in the specification parameters and/or acceptance criteria of the primary packaging of the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
a) Tightening of specification acceptance criteria	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 for safety or quality reasons	–	1, 2, 3, 4, 6	IB

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification acceptance criteria (e.g. made during the procedure for the marketing authorization of a medicinal product or a type II variation procedure) unless it has been previously reviewed 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 pharmaceutical ingredient.
3. Any change should be within the range of currently approved acceptance criteria.
4. The analytical procedure remains the same, or changes in the analytical procedure are minor.
5. Any new test method is based on the general analysis methods described in the Pharmacopoeia of the Union or otherwise in the pharmacopoeia of a Member State or otherwise any other pharmacopoeia according to the Concept (e.g., HPLC, spectrophotometry, titrimetry, etc.).

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical procedure and validation data, where relevant.
4. Batch analysis data on two batches of the packaging material for all specification parameters.
5. Justification/risk assessment from the marketing authorization holder or the APIMF 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 APIMF holder, as appropriate, of the new specification parameter and the acceptance criteria.

B.I.c.3. Change in the analytical test procedure for the primary packaging of the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
a) Minor changes to an approved analytical procedure	1, 2, 3	1, 2	IA
b) Other changes to an analytical procedure (including replacement or addition)	1, 3, 4	1, 2	IA
c) Deletion of an analytical procedure if an alternative analytical procedure is already authorized	5	1	IA

Conditions
1. Appropriate validation studies have been performed according to the acts of the Union's governing bodies in the field of medicines circulation and show that the updated analytical procedure is at least equivalent to the former analytical procedure.
2. The method of analysis remains the same (e.g. a change in column length or temperature, but not a different type of column or method).
3. No new test method concerns a novel non-standard technique or a standard technique used in a novel way.
4. The active pharmaceutical ingredient/medicinal product is not biological.
5. There is still an analytical procedure registered for the specification parameter.

Documentation
1. Amendment to the relevant section(s) of the marketing authorization application, 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 analytical procedure.

B.I.c.4. Change in a component of the secondary packaging of the active pharmaceutical ingredient (including replacement or addition), if specified in the marketing authorization application	Conditions to be fulfilled	Documents and data	Procedure
	1, 2, 3, 4	1	IA

Conditions
1. The secondary packaging is not functional to ensure the stability of the active pharmaceutical ingredient or is at least equivalent in its protective properties to the approved one.
2. The replacement packaging component must be suitable for storing the active pharmaceutical ingredient under approved storage conditions.
3. The replacement must not be due to a critical defect in the packaging component.
4. The change is not the result of unexpected circumstances arising during manufacture or storage of the active pharmaceutical ingredient.

Documentation
1. Amendment of the relevant section(s) of the marketing authorization application.

B.I.d) Stability

B.I.d.1. Change in the retest period/storage period or storage conditions of the active pharmaceutical ingredient where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved marketing authorization application	Conditions to be fulfilled	Documents and data	Procedure
a) Retest period/storage period			
1. Reduction of the retest period	1	1, 2, 3	IA
2. Extension of the retest period based on extrapolation of stability data not in accordance with the acts of the Union's governing bodies in the field of medicines circulation<*>	–	–	II
3. Extension of storage period of a biological active pharmaceutical ingredient 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 pharmaceutical ingredient	1	1, 2, 3	IA
2. Change in storage conditions of biological active pharmaceutical ingredients, when the stability studies have not been performed in accordance with a currently approved stability protocol	–	–	II
3. Change in storage	–	1, 2, 3	IB

conditions of the active pharmaceutical ingredient			
c) Change of the approved stability study program	1, 2	1, 4	IA
Conditions 1. The change should not be the result of unexpected events arising during manufacture or of a stability change. 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 marketing authorization application. 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 batches of the active pharmaceutical ingredient 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 conducted in accordance with the currently approved program. The study results must show that the agreed relevant specifications are still met. 3. Copies of approved specifications of the active pharmaceutical ingredient or link to the relevant document in the marketing authorization application. 4. Justification for the proposed changes.			
<*> Note	Retest period not applicable for biological active pharmaceutical ingredients.		

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 pharmaceutical ingredient, concerning:	Conditions to be fulfilled	Documents and data	Procedure
a) One unit operation in the manufacturing process of the active pharmaceutical ingredient, including the resulting in-process controls and/or analytical procedures	–	1, 2, 3	II
b) Analytical procedures for starting materials/reagents/ intermediates and/or the active pharmaceutical ingredient	–	1, 2, 3	II

Documentation
1. The design space has been developed in accordance with the acts of the Union's governing bodies in the field of medicines circulation and international scientific guidelines. Results from product, process and analytical development studies (e.g. interaction of the different parameters forming the design space to be studied, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic mechanistic understanding of material attributes, process parameters and the critical quality attributes of the active pharmaceutical ingredient 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 marketing authorization application.

B.I.e.2. Introduction of a post-approval change management protocol related to the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
	–	1, 2, 3	II

Documentation
1. Detailed description for the proposed change.
2. Change management protocol related to the active pharmaceutical ingredient.
3. Amendment of the relevant section(s) of the marketing authorization application.

B.I.e.3. Deletion of an approved change management protocol related to the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
	1	1, 2	IA_{IN}

Conditions
1. The deletion of the approved change management protocol related to the active pharmaceutical ingredient 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 marketing authorization application.

Documentation
1. Justification for the proposed deletion.
2. Amendment of the relevant section(s) of the marketing authorization application.

B.I.e.4. Changes to an approved change management	Conditions to be fulfilled	Documents and data	Procedure

protocol			
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. A declaration of the manufacturer's qualified person that any change should be within the range of currently approved acceptance criteria. In addition, a declaration that an assessment of comparability is not required for biological medicinal products.			
B.I.e.5. Implementation of changes provided for in an approved change management protocol	Conditions to be fulfilled	Documents and data	Procedure
a) The implementation of the change requires no further supportive data	1	1, 3	IA_{IN}
b) The implementation of the change requires further supportive data	–	1, 2, 3	IB
c) Implementation of a change for a biological medicinal product	–	1, 2, 3, 4	IB
Conditions 1. The proposed change has been performed fully in accordance with the approved change management protocol.			
Documentation 1. A declaration that the change is in accordance with the approved change management protocol and that the study results meet the acceptance criteria specified in the protocol. In addition, a declaration that an assessment of comparability is not required for biological medicinal products. 2. Results of the studies performed in accordance with the approved change management protocol. 3. Amendment of the relevant section(s) of the marketing authorization application. 4. Copies of approved specifications of the active pharmaceutical ingredient or link to the relevant section in the marketing authorization application.			

B.II. 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	Documents and data	Procedure
a) Changes in imprints, bossing or other markings	1, 2, 3, 4	1	IA
b) Changes in scoring/break lines intended to divide into equal doses	–	1, 2, 3	IB
Conditions 1. Medicinal 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 marketing authorization application, including a detailed drawing or written description of the current and new appearance and revised product information as appropriate. 2. Subject to agreement with the expert organization, samples of the medicinal product and/or their visual image to assess the appearance. 3. Results of the appropriate tests demonstrating equivalence in characteristics/dosing accuracy and conducted under the Pharmacopoeia of the Union or otherwise the Pharmacopoeia of a Member State or otherwise any other pharmacopoeia according to the Concept.			
B.II.a.2 Change in the shape or dimensions of the dosage form	Conditions to be fulfilled	Documents and data	Procedure
a) Immediate release tablets, capsules, suppositories and pessaries	1, 2, 3, 4	1, 4	IA
b) Gastro-resistant, modified or prolonged release dosage 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 medicinal product with the new dosage form or dosage form dimensions is comparable to the dissolution profile of the medicinal product with the old dosage form or dosage form dimensions. For herbal medicinal products, where equivalence dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one. 2. Medicinal product release and end-of-shelf life specifications have not been changed (except for dosage form 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 marketing authorization application, including a detailed drawing of the authorized and proposed dosage form and 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 in accordance with the Rules for Conducting Bioequivalence Studies). For herbal medicinal products, comparative disintegration data may be acceptable. 3. Justification for not submitting a new bioequivalence study according to the Rules for Conducting Bioequivalence Studies. 4. Samples of the medicinal product and/or its visual image, where applicable, subject to agreement with the expert organization. 5. Results of the appropriate tests demonstrating equivalence in characteristics/dosing accuracy and conducted under the Pharmacopoeia of the Union or otherwise the Pharmacopoeia of a Member State or otherwise any other pharmacopoeia according to the Concept.

<*> Note	For B.II.a.2.c), any change to the strength of the medicinal product requires the submission of an extension application, with the exception of aligning the marketing authorization application with the Union requirements if the new strength is authorized in accordance with the legislation of a Member State in only one of the Member States stated as part of the alignment procedure.

B.II.a.3. Changes in the composition (excipients) of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Changes in components of the flavoring or coloring system			
1. Addition, deletion or replacement	1, 2, 3, 4, 5, 6, 7, 9, 10	1, 2, 4, 5, 6	IA

2. Increase or reduction	1, 2, 3, 4, 10	1, 2, 4	IA
b) Other excipients			
1. Any minor adjustment of the quantitative composition of the medicinal 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 medicinal 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 and/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 dosage 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 dosage form.
3. The medicinal 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 (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot or industrial batches and at least three 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 the marketing authorization holder will report to the

authorized authority the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions). In addition, where relevant, photostability testing should be performed.

5. Any new proposed components must comply with the requirements of the Union's regulatory acts for colors for use in foodstuffs and flavors.
6. No new component involves the use of materials of human or animal origin for which assessment is required of viral safety data or compliance with the current requirements of the Pharmacopoeia of the Union (and/or other pharmacopoeias according to the Concept) on minimizing the risk of transmitting animal spongiform encephalopathy agents via human medicinal products.
7. Where applicable, the change does not affect the possibility of differentiation between strengths and does not have a negative impact on taste acceptability for pediatric formulations.
8. The dissolution profile of the new medicinal product determined on a minimum of two pilot scale batches is comparable to the old one (no significant differences regarding dissolution profile comparability in accordance with the Rules for 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. possibility of differentiation between strengths.
10. The product concerned is not a biological medicinal product.

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application, including the identification test method for any new colorant, where relevant, and revised product information as appropriate.
2. Proof from the marketing authorization holder that the required stability studies have been started (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 the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).
3. The results of stability studies on the relevant stability parameters on at least two pilot or industrial batches, covering a minimum period of three months, and an assurance that these studies will be finalized and that the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).
4. Samples of the medicinal product and/or its visual image, where applicable, subject to agreement with the expert organization.
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

authorized authority and shown to comply with the scope of the current monograph of the Pharmacopoeia of the Union (or other pharmacopoeias according to the Concept) on minimizing the risk of transmitting animal spongiform encephalopathy agents via human 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 analytical procedures of the medicinal product specification, 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 medicinal product in the new and old composition. For herbal medicinal products, comparative disintegration data may be sufficient.
9. Justification for not submitting a new bioequivalence study in accordance with the Rules for Conducting Bioequivalence Studies.

B.II.a.4. Change in the coating weight of oral dosage forms or change in the weight of capsule shells	Conditions to be fulfilled	Documents and data	Procedure
a) Solid oral dosage forms	1, 2, 3, 4	1, 2	IA
b) Gastro-resistant, modified or prolonged release dosage forms where the coating is a critical factor for the release mechanism	–	–	II

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 medicinal product specification has only been updated in respect of weight and dimensions, if applicable.
4. Stability studies have been started with at least two pilot scale or industrial scale batches, and at least three months satisfactory stability data are at the disposal of the applicant at the time of implementation, and an assurance is given that these studies will be finalized. The marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application. 2. A declaration from the marketing authorization holder that the required stability studies have been started (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the marketing authorization holder 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 the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions). In addition, where relevant, photostability testing should be performed.			
B.II.a.5. Change in concentration of a single-dose, total use parenteral product, where the amount of active pharmaceutical ingredient per unit dose (i.e. the strength) remains the same	Conditions to be fulfilled	Documents and data	Procedure
	–	–	II
B.II.a.6. Deletion of the solvent/diluent container from the pack	Conditions to be fulfilled	Documents and data	Procedure
	–	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 medicinal product information.			

B.II.b) Manufacture

B.II.b.1. Replacement or addition of a manufacturing site for a part or all of the manufacturing process of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
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, 10	IA
c) Site where any manufacturing operation(s)	–	–	II

take place, except batch release, batch control, and secondary packaging, for biological medicinal products or for dosage forms manufactured by complex production processes			
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, 10	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 medicinal products	–	1, 2, 3, 4, 5, 7, 8, 10	IB

Conditions

1. Satisfactory inspection in the last three years by the inspection authorities of the Member States or of a country with which an operational agreement exists on mutual recognition of Good Manufacturing Practice certificates.
2. Site appropriately authorized (to manufacture the dosage form or product concerned).
3. The product concerned is not a sterile product.
4. Where relevant, for instance, for suspensions and emulsions, the process validation plan is available or validation of the manufacture at the new site has been successfully carried out in accordance with the current protocol with at least three production batches.
5. The product concerned is not a biological medicinal product.

Documentation

1. Proof that the proposed site is appropriately authorized for the dosage form or product concerned.
2. Where relevant, the batch numbers, corresponding batch size and the manufacturing date of batches (≥ 3) used in the validation study should be indicated and the validation data presented or validation protocol submitted.
3. The paragraph of the variation application form on changes (cover letter or

variation application form attached to the cover letter) should clearly outline the previously approved and proposed manufacturers as listed in Section 2.5 of the application form.

4. Copies 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 (including the equivalence dissolution test in appropriate cases) on the last three batches from the previous site. Batch data on the next two full production batches should be made available upon request and reported if outside specification (with proposed actions).
6. For semi-solid and liquid dosage forms in which the active pharmaceutical ingredient 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 pharmaceutical ingredient as a starting material — a declaration by the qualified person at the site responsible for batch release that the active pharmaceutical ingredient is manufactured in accordance with the Rules of Good Manufacturing Practice for starting materials.
8. Amendment of the relevant section(s) of the marketing authorization application.
9. If the manufacturing site and the primary packaging site are different, conditions of transportation and bulk storage should be specified and validated.
10. Valid document certifying the compliance of the finished dosage form manufacturing site(s) with the requirements of the Union's Good Manufacturing Practice.

Notes:	Declarations of an qualified person concerning an active pharmaceutical ingredient Manufacturing authorization holders are obliged to only use as starting materials active pharmaceutical ingredients that have been manufactured in accordance with the Rules of Good Manufacturing Practice, so a declaration is expected from each of the manufacturing authorization holders that use the active pharmaceutical ingredient as a starting material. In addition, as the qualified person responsible for batch certification takes overall responsibility for each batch, a further declaration from the qualified person responsible for batch certification is expected when the batch release site is a different site from the dosage form manufacturer. In many cases only one manufacturing authorization holder is involved and therefore only one declaration shall 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 qualified person. This will be accepted provided that: The declaration makes it clear that it is signed on behalf of all

	the involved qualified persons. The arrangements are underpinned by a technical agreement as described in Chapter 7 of the Rules of Good Manufacturing Practice, and the qualified person providing the declaration is the one identified in the agreement as taking specific responsibility for the compliance of the active pharmaceutical ingredient manufacturer(s) with the Rules of Good Manufacturing Practice. Note: these arrangements are subject to inspection by the authorized authorities.

B.II.b.2. Change of the manufacturer responsible for the quality control of the medicinal product and the batch release of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Replacement or addition of a site where batch control/testing takes place	1, 2, 3	3, 4	IA
b) Replacement or addition of a site where batch control/testing takes place for a biological medicinal product and any of the test methods performed at the site is a biological/immunological/ immunochemical method			II
c) Replacement or addition of a manufacturer responsible for batch release			
1. Not including batch control/testing	1	1,2,3	IA_{IN}
2. Including batch control/testing	1, 2	1,2,3	IA_{IN}
3. Including batch control/testing for a biological medicinal product and any of the test methods performed at that site is a biological/ immunological/ immunochemical method			II

Conditions
1. The site is appropriately authorized.
2. The product is not a biological medicinal product.
3. The transfer of analytical procedures from the old to the new testing laboratory has been successfully completed.

Documentation
1. The cover letter or variation application form attached to the cover letter should clearly outline the previously approved and proposed manufacturers.
2. A declaration by the qualified person responsible for batch release stating that active pharmaceutical ingredient manufacturers referred to in the marketing authorization application operate in accordance with the Rules of Good Manufacturing Practice for starting materials. A single declaration may be acceptable under certain circumstances (see the note under variation B.II.b.1).
3. Amendment of the relevant section(s) of the marketing authorization application, including product information and, as appropriate, data on the validation (verification) of analytical procedures transferred from the old site to the new one, in accordance with the acts of the Union's governing bodies in the field of transfer of technologies and analytical procedures.
4. Valid document certifying the compliance of the finished dosage form manufacturing site(s) carrying out batch release with the Rules of Good Manufacturing Practice

B.II.b.3. Change in the manufacturing process of the medicinal product, including an intermediate used in the manufacture of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Minor change in the manufacturing process	1, 2, 3, 4, 5, 6, 7	1, 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 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 pharmaceutical ingredient	–	–	II
f) Minor change in the manufacturing process of an aqueous oral suspension and other specialized dosage forms	–	1, 2, 4, 6, 7, 8	IB
g) Change in the medicinal product manufacturing process: relocation of sterile filtration from the Grade A/B area to the Grade C area	–	–	II
h) Change in the secondary packaging material of a bulk product that does not come into direct contact with this product (including replacement and addition)	8	1	IA

Conditions

1. No change in the qualitative and quantitative impurity profile or in physico-chemical properties.
2. The change relates to:
   an immediate release solid oral or topical dosage form;
   liquid dosage forms in the form of solutions, semi-solid dosage forms and suppositories that do not belong to specialized dosage forms manufactured by non-standard processes in accordance with the acts of the Union's governing bodies in the field of medicines circulation. Moreover, the change relates to process parameter(s) that have been considered to have no impact on the quality of the medicinal product (regardless of the type of medicinal product and/or dosage form) and the medicinal product concerned is not a biological or herbal medicinal product.
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 acceptance criteria) are required to these controls.
5. The specifications of the medicinal 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 Union's relevant documents have been started with at least one pilot or industrial batch, and at least three months stability data are at the disposal of the applicant. Assurance is given that the studies will be finalized and that the marketing authorization holder

will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).
8. The secondary packaging is not functional to ensure the stability or is at least equivalent in relevant properties to the approved one.

Documentation
1. Amendment of the relevant section(s) of the marketing authorization application.
2. For semi-solid and liquid dosage forms in which the active pharmaceutical ingredient 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. Batch data on the next two full production batches should be made available upon request or reported if outside specification (with proposed actions). For herbal medicinal products, comparative disintegration data may be sufficient.
4. Justification for not submitting a new bioequivalence study in accordance with the Union Rules for Conducting Bioequivalence Studies.
5. For changes to process parameter(s) that have been considered to have no impact on the quality of the medicinal product, a declaration to this effect reached in the context of the previously approved risk assessment.
6. Copies of release and end-of-shelf life specifications (in the form of a link to the relevant document in the dossier sequence or an annex to the cover letter).
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 if outside specification (with proposed actions).
8. Proof from the marketing authorization holder that relevant stability studies have been started (with indication of the batch numbers concerned) and relevant stability parameters have been assessed in at least one pilot or industrial batch and at least three 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 the studies will be finalized and that the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).

B.II.b.4. Change in the batch size (including batch size ranges) of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Up to 10-fold increase compared to the originally approved batch size	1, 2, 3, 4, 5, 7	1, 4	IA

b) Up to 10-fold decrease compared to the originally approved batch size	1, 2, 3, 4, 5, 6	1, 4	IA
c) The change requires assessment of the comparability of a biological medicinal product or the change in batch size requires a new bioequivalence study	–	–	II
d) The change relates to all other dosage forms manufactured by complex manufacturing processes	–	–	II
e) More than 10-fold increase compared to the originally approved batch size for immediate release (oral) dosage forms	–	1, 2, 3, 4, 5, 6	IB
f) The scale for a biological 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 dosage forms or to non-sterile liquid dosage 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 industrial batches at the proposed new batch size in accordance with the relevant guidelines.
5. The product concerned is not a biological medicinal product.
6. The change should not be the result of unexpected events arising during manufacture or of a stability change.
7. The batch size is within the 10-fold range of the batch size provided for 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 marketing authorization application.

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 (including the equivalence dissolution test in appropriate cases). Batch data on the next two full production batches should be made available upon request and reported by the MAH if outside specification (with proposed actions).
3. Copies of approved release and end-of-shelf life specifications (in the form of a link to the relevant document in the dossier sequence or an annex to the cover letter).
4. Where relevant, the numbers of batches, a new 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 on the relevant stability parameters on at least one pilot or industrial batch, covering a minimum period of three months, and an assurance that these studies will be finalized and that the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions). For biological medicines: a declaration that an assessment of comparability is not required.

B.II.b.5. Change to in-process tests or acceptance criteria applied during the manufacture of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Tightening of in-process acceptance criteria	1, 2, 3, 4	1, 2	IA
b) Addition of a new test(s) and acceptance criteria	1, 2, 5, 6	1, 2, 3, 4, 5, 7, 8	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 medicinal product	–	–	II
e) Widening of the approved in-process control acceptance criteria, which may have a significant effect on the overall quality of the medicinal product	–	–	II
f) Addition or replacement of	–	1, 2, 3, 4,	IB

an in-process test for safety or quality reasons		5, 7, 8	
g) Minor change to the analytical procedure of in-process control	4, 6, 8, 9	1, 2, 3	IA

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification acceptance criteria (e.g. made during the procedure for marketing authorization 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 acceptance criteria.
4. The method of analysis remains the same, and the analytical procedure remains the same, or changes in the analytical procedure are minor (e.g. a change in column length or temperature, but not a different type of column).
5. No new test method concerns 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 pharmaceutical ingredient (except for 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 or tapped density, etc.);
   identity test (unless there is a suitable alternative control already present);
   microbiological control (unless not required for the particular dosage form).
8. Appropriate validation studies have been performed in accordance with the acts of the Union's governing bodies in the field of medicines circulation and show that the updated analytical procedure is at least equivalent to the former analytical procedure.
9. The limits of the total impurities are not changed, and no new unqualified impurities are detected.

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application.
2. Comparative table of current and proposed in-process tests and acceptance criteria or comparative table of changes in the analytical procedure.
3. Details of any new analytical procedure and validation data (where relevant) confirming that the updated analytical procedure is at least equivalent to the previous one.
4. Batch analysis data on two production batches (three production batches for biologicals, unless otherwise justified) of the medicinal product for all

specification parameters.
5. Where appropriate, comparative dissolution profile data for the medicinal product on at least one pilot batch manufactured using the current and new in-process tests.
6. For herbal medicinal products, comparative disintegration data may be sufficient.
7. Justification/risk assessment showing that the in-process test is non-significant or that it is obsolete.
8. Justification of the new in-process test and acceptance criteria.

B.II.c) Control of excipients

B.II.c.1. Change in the specification parameters and/or acceptance criteria of an excipient	Conditions to be fulfilled	Documents and data	Procedure
a) Tightening of specification acceptance criteria	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	1, 2, 7	IA
d) Change outside the approved range of specification acceptance criteria	–	–	II
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the medicinal product	–	–	II
f) Addition or replacement (excluding a biological medicinal product) of a specification parameter with its corresponding test method for safety or quality reasons	–	1, 2, 3, 4, 5, 6, 8	IB
g) Where there is no	–	1, 2, 3, 4,	IB

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 pharmacopoeia according to the Concept or otherwise a pharmacopoeia not covered by the Concept		5, 6, 8	

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification acceptance criteria (e.g. made during the procedure for the marketing authorization of the medicinal product 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 acceptance criteria.
4. The analytical procedure remains the same, or changes in the analytical procedure are minor.
5. No new test method concerns 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 pharmaceutical ingredient (except for 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);
   any critical physical characteristics (particle size, bulk or 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 marketing authorization application.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical procedure and validation data, where relevant.
4. Batch analysis data on two production batches (three production batches for biologicals, unless otherwise justified) of the excipient for all specification parameters.
5. Where appropriate, comparative dissolution profile data for the medicinal 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 sufficient.
6. Justification for not submitting a new bioequivalence study in accordance with the Rules for Conducting Bioequivalence Studies.
7. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.
8. Justification of the new specification parameter and acceptance criteria.

B.II.c.2. Change in the analytical procedure for an excipient	Conditions to be fulfilled	Documents and data	Procedure
a) Minor changes to an approved analytical procedure	1, 2, 3, 4	1, 2	IA
b) Deletion of an analytical procedure if an alternative analytical 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 an analytical procedure (including replacement or addition)	–	1, 2	IB

Conditions 1. Appropriate validation studies have been performed in accordance with the relevant documents and show that the updated analytical procedure is at least equivalent to the former analytical procedure. 2. There have been no changes of the total impurity limits; no new unqualified impurities have been detected. 3. The method of analysis remains the same (e.g. a change in column length or temperature, but not a different type of column or method). 4. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent (except for standard pharmacopoeial microbiological methods). 5. An alternative analytical procedure is already authorized for the specification parameter.			
Documentation 1. Amendment to the relevant section(s) of the marketing authorization application, 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 analytical procedure.			
B.II.c.3. Change in the source of an excipient or reagent with TSE risk	Conditions to be fulfilled	Documents and data	Procedure
a) From TSE risk material to vegetable or synthetic origin			
1. For excipients or reagents not used in the manufacture of a biological active pharmaceutical ingredient or in a biological medicinal product	1	1	IA
2. For excipients or reagents used in the manufacture of a biological active pharmaceutical ingredient or in a biological 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	–	–	II

TSE Certificate of Suitability			
c) Change in the source of an excipient with a low risk of TSE contamination	2	1, 2	IA
Conditions 1. Excipient and medicinal product release and end-of-shelf life specifications remain the same. 2. It is necessary to ensure compliance with the conditions for minimizing the risk of TSE contamination, as specified in the acts of the Union's governing bodies in the field of medicines circulation.			
Documentation 1. Proof 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 medicinal product.			
B.II.c.4. Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the marketing authorization application) or a novel excipient	Conditions to be fulfilled	Documents and data	Procedure
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 physico-chemical properties of the excipient which may affect the quality of the medicinal product	-	-	II
c) The excipient is a biological substance	-	-	II
d) Deletion of one manufacturing process of a non-pharmacopoeial excipient (when described in the marketing authorization application for the medicinal product) or a novel excipient	3, 4	1, 4, 5	IA

Conditions 1. The synthetic route and specifications are identical and there is no change in the qualitative and quantitative impurity profile (excluding residual solvents, provided they are controlled in accordance with the limits specified in the acts of the Union's governing bodies in the field of medicines circulation) or in physico-chemical properties. 2. The excipient is not an adjuvant. 3. At least one previously approved production process must remain unchanged. 4. The deletion should not be due to critical deficiencies concerning manufacturing.
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application. 2. Batch analysis data (in comparative tabular 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 medicinal product on at least two batches (minimum pilot scale). For herbal medicinal products, comparative disintegration data may be sufficient. 4. Copies of approved and new (if applicable) specifications of the excipient. 5. Proof from the applicant that the deletion is not due to critical deficiencies concerning manufacturing.

B.II.d) Control of the medicinal product

B.II.d.1. Change in the specification parameters and/or acceptance criteria of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Tightening of specification acceptance criteria	1, 2, 3, 4	1, 2	IA
b) Tightening of acceptance criteria for immunological medicinal products or human plasma-derived medicinal products subject to batch release by the official control authority of a Member State	1, 2, 3, 4	1, 2	IAIN
c) Addition of a new specification parameter to the specification with its corresponding test method and/or procedure			II
d) Deletion of a non-significant	1, 2, 7	1, 2, 4	IA

specification parameter (e.g. deletion of an obsolete parameter)			
e) Change outside the approved range of specification acceptance criteria	–	–	II
f) Deletion of a specification parameter which may have a significant effect on the overall quality of the medicinal product	–	–	II
g) Addition or replacement of a specification parameter with its corresponding test method for safety or quality reasons	–	–	II
h) Update of the dossier, including the normative document, to comply with the provisions of an updated general monograph of the Pharmacopoeia of the Union or (for the marketing authorization of the medicinal product in one Member State) the pharmacopoeia of a Member State (including the update of references) for the medicinal product <*>	1, 2, 3, 4, 5, 6	1, 2	IAIN
i) the test according to Monograph 2.1.9.14 of the Pharmacopoeia of the Union "Uniformity of Dosage Units" is introduced to replace the previously approved method or test according to Monograph 2.1.9.5 "Uniformity of Mass of Single-Dose Preparations"	1, 2, 8	1, 2, 3	IA
j) Reduction in the frequency of routine testing up to the deletion of testing or periodic testing (e.g. microbiological testing of the medicinal		1, 2, 5	IB

product)			
k) Change in the specification parameters and/or limits of the medicinal product to more accurately describe the appearance of the medicinal product	2	1, 2	IA

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification acceptance criteria (e.g. made during the procedure for the marketing authorization of the medicinal product or a type II variation procedure).
2. The change does not result from unexpected events arising during the manufacture (e.g. new unqualified impurity; change in total impurity limits) or testing of the medicinal product.
3. Any change should be within the range of currently approved acceptance criteria.
4. The procedure remains the same, or changes in the procedure are minor.
5. The change does not concern any impurities (including genotoxic) or dissolution.
6. The change concerns the updating of the acceptance criteria for microbial control to be in line with the current Pharmacopoeia of the Union or otherwise the pharmacopoeia of a Member State or otherwise any other pharmacopoeia according to the Concept, and the currently registered acceptance criteria for microbial control do not include any additional specified controls over the Pharmacopoeia requirements for the particular dosage form.
7. The specification parameter does not concern a critical parameter, e.g.:
   assay;
   impurities (unless a particular solvent is definitely not used in the manufacture of the medicinal product);
   any critical physical characteristics (hardness or friability for uncoated tablets, dimensions, etc.);
   any request for skip testing.
8. The proposed control is fully in line with the Table 2.1.9.14.-1 of the monograph of the Pharmacopoeia of the Eurasian Economic Union "Uniformity of Dosage Units" and does not include the alternative proposal for testing uniformity by mass variation instead of content uniformity when the latter is specified in the above table.

Documentation 1. Amendment of the relevant section(s) of the marketing authorization application. 2. Comparative table of current and proposed specifications. 3. Batch analysis data on two production batches (three production batches for biologicals, unless otherwise justified) of the medicinal product for all specification parameters. 4. Justification/risk assessment showing that the parameter is non-significant. 5. Justification/risk assessment showing that the frequency of testing for a parameter may be changed.	
<*> Note	There is no need to notify the authorized authorities of an updated monograph of the Pharmacopoeia of the Union or the pharmacopoeia of a Member State (for the marketing authorization of the medicinal product in one Member State) in the case that reference is made to the "current edition (in accordance with the legislation of a Member State)" in the marketing authorization application and/or the normative document of an authorized medicinal product. This variation therefore applies to cases where no reference to the updated monograph of the pharmacopoeia was contained in the marketing authorization application and/or the normative document and the variation is made to make reference to the updated version.

B.II.d.2. Change in the analytical procedure for the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Minor changes to an approved analytical procedure	1,2,3	1	IB
b) Deletion of an analytical procedure if an alternative analytical procedure is already authorized	3	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 an analytical procedure (including	–	–	II

replacement or addition)			
e) Update of the analytical procedure to comply with the updated general monograph in the Pharmacopoeia of the Union or the pharmacopoeia of a Member State (for the marketing authorization of the medicinal product in one Member State)	1,2,3,4	1	IA
f) To reflect compliance with the Pharmacopoeia of the Union or the pharmacopoeia of a Member State (for the marketing authorization of the medicinal product in one Member State) and remove reference to the outdated internal analytical procedure and its number <*>	1,2,3,4	1	IA

Conditions

1. There have been no changes of the total impurity limits; no new unqualified impurities have been detected.
2. There are no significant changes affecting the reproducibility of the analytical procedure.
3. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (except for standard pharmacopoeial microbiological methods).
4. The registered analytical procedure already refers to the general monograph of the Pharmacopoeia of the Union or the pharmacopoeia of a Member State (for the marketing authorization of the medicinal product in one Member State), and any changes are minor in nature and require the technical update of the marketing authorization application.

Documentation

1. Amendment to the relevant section(s) of the marketing authorization application, including a description of the analytical procedure, revised specifications for impurities (if applicable).

<*> Note	There is no need to notify the authorized authorities of an updated monograph of the Pharmacopoeia of the Union or the pharmacopoeia of a Member State in the case that reference is made to the "current edition (in accordance with the legislation of a Member State)" in the dossier of an authorized medicinal product.

B.II.d.3. Variations related to the introduction of real-time release or parametric release in the manufacture of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
	–	–	II

B.II.e) Packaging (closure) system

B.II.e.1. Change in primary packaging of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Qualitative and/or quantitative composition of the material of the packaging (closure) system (primary packaging)			
1. Solid dosage forms	1, 2, 3	1, 2, 3, 4, 6	IA
2. Semi-solid and non-sterile liquid dosage forms	–	1, 2, 3, 5, 6	IB
3. Sterile medicinal products and biological 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 the primary packaging type or addition of a new primary packaging type			
1. Solid, semi-solid and non-sterile liquid dosage forms	–	1, 2, 3, 5, 6, 7	IB
2. Sterile medicinal products and biological medicinal products	–	–	II
3. Deletion of a primary packaging type that does not lead to the complete deletion of a strength or dosage form	4	1, 8	IA

Conditions

1. The change only concerns the same packaging 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, and relevant stability parameters have been assessed in at least two pilot scale or industrial batches, and at least three 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 three months' stability data do not yet have to be available. These studies must be finalized, and the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).
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 marketing authorization application.
2. Appropriate data on the new packaging (e.g. comparative data on permeability, e.g. for O_2, CO_2, moisture, etc.).
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 the acts of the Union's governing bodies on the safety of materials in contact with food products.
4. A declaration from the marketing authorization holder that the required stability studies have been started (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 the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).
5. The results of stability studies on the relevant stability parameters on at least two pilot or industrial batches, covering a minimum period of three months, and an assurance that these studies will be finalized and that the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).
6. Comparison of current and proposed primary packaging specifications, if applicable.
7. Photo and/or sketch of the new packaging (closure) system where applicable.
8. A declaration from the marketing authorization holder 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), any change which results in a "new dosage form" requires the submission of an extension application.		
B.II.e.2. Change in the specification parameters and/or acceptance criteria of the primary packaging of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Tightening of specification acceptance criteria	1, 2, 3, 4	1, 2	IA
b) Addition of a new specification parameter to the specification with its corresponding analytical procedure	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 for safety or quality reasons	–	1, 2, 3, 4, 6	IB
e) Widening of the acceptance criteria for the Total Thickness parameter of the blister foil (covering aluminum foil) in the primary packaging of solid dosage forms caused by the difference in the amount of primer material applied	6, 7	1, 2, 4, 5, 6, 7	IA

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification acceptance criteria (e.g. made during the procedure for the marketing authorization of the medicinal product 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 acceptance criteria.
4. The analytical procedure remains the same, or changes in the analytical procedure are minor.

5. Any new test procedure is based on the general analysis methods described in the Pharmacopoeia of the Union or the pharmacopoeia of a Member State (for the marketing authorization of the medicinal product in one Member State) (e.g., HPLC, spectrophotometry, titrimetry, etc.).
6. The primer material remains the same.
7. Relevant stability studies in accordance with the acts of the Union's governing bodies in the field of medicines circulation have been started with at least two pilot or industrial batches. These studies must be finalized, and data will be provided immediately to the authorized authorities if outside specifications or potentially outside specifications at the end of the approved shelf life.

Documentation
1. Amendment of the relevant section(s) of the marketing authorization application.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical procedure and validation data, where relevant.
4. Batch analysis data on two batches of the packaging material for all specification parameters.
5. Justification/risk assessment showing that the parameter is non-significant.
6. Justification of the new specification parameter and acceptance criteria.
7. Proof that relevant stability studies in accordance with the acts of the Union's governing bodies in the field of medicines circulation have been started with at least two pilot or industrial batches.

B.II.e.3. Change in the analytical procedure for the primary packaging of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Minor changes to an approved analytical procedure	1, 2, 3	1, 2	IA
b) Other changes to an analytical procedure (including replacement or addition)	1, 3, 4	1, 2	IA
c) Deletion of an analytical procedure if an alternative analytical procedure is already authorized	5	1	IA

Conditions

1. Appropriate validation studies have been performed according to the relevant acts of the Union's governing bodies in the field of medicines circulation and show that the updated analytical procedure is at least equivalent to the former analytical procedure.
2. The method of analysis remains the same (e.g. a change in column length or temperature, but not a different column or method).
3. No new test method concerns a novel non-standard technique or a standard technique used in a novel way.
4. The active pharmaceutical ingredient/medicinal product is not biological.
5. An alternative analytical procedure is already authorized for the specification parameter.

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application.
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 analytical procedure.

B.II.e.4. Change in the shape or dimensions of the packaging (closure) system (primary packaging)	Conditions to be fulfilled	Documents and data	Procedure
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 medicinal product	–	–	II
c) Sterile medicinal products	–	1, 2, 3, 4	IB

Conditions

1. No change in the qualitative or quantitative composition of the primary packaging material.
2. The change does not concern a fundamental part of the packaging material which may have an impact on the delivery, use, safety or stability of the medicinal product.
3. In case of a change in the headspace or a change in the surface/volume ratio, stability studies have been started and relevant stability parameters have been assessed in at least two pilot (three for biological medicinal products) or industrial batches and at least three months (six months for biological medicinal products) stability data are at the disposal of the applicant. Assurance is given that the studies will be finalized and that the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application, including the description, detailed drawing and composition of the primary packaging or closure material and revised product information as appropriate.
2. Photo and/or sketch of the new packaging (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 from the marketing authorization holder that the required stability studies have been started (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 the time of implementation for a Type IA notification and the 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 the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).

B.II.e.5. Change in the pack size of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Change in the number of dosage form units (e.g. tablets, ampoules, etc.) in a pack			
1. Change within the range of the currently approved pack sizes	1, 2	1, 3	IAIN

2. Change outside the range of the currently approved pack sizes		1, 2, 3	IB
b) Deletion of the pack size(s)	3	1, 2	IAIN
c) Change in the fill weight/fill volume of sterile multi-dose (or single-dose, partial use) parenteral medicinal products, including biological medicinal products	–	–	II
d) Change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) medicinal products	–	1, 2, 3	IB

Conditions
1. A 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 marketing authorization application, including revised product information as appropriate.
2. Justification showing that the new/remaining pack sizes are consistent with the dosage regimen and duration of treatment as approved in the summary of product characteristics.
3. A declaration that stability studies will be conducted in accordance with the acts of the Union's governing bodies in the field of medicines circulation where stability parameters could be affected. Data to be reported only if outside specifications (with proposed actions).

Note:	For B.II.e.5.c) and B.II.e.5.d), 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 packaging (material) not in contact with the medicinal product (such as the color of flip-off caps, color code rings on ampoules, the change of needle shield (different plastic used), the change of the design (color) of	Conditions to be fulfilled	Documents and data	Procedure

intermediate or secondary packaging mock-ups, barcode application (2D, 3D) or Braille font application))			
a) Change that affects the product information specified in paragraph 1.6.1 of Appendix 19 to the Rules of Marketing Authorization	1	1	IA_{IN}
b) Change that does not affect the product information specified in paragraph 1.6.1 of Appendix 19 to the Rules of Marketing Authorization	1	1	IA
Conditions 1. The change does not concern a part of the packaging material which may have an impact on the delivery, use, safety or stability of the medicinal product.			
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application, including revised product information as appropriate.			
B.II.e.7. Change in a manufacturer of components of the packaging (closure) system (primary packaging) or additional products (including devices and component parts) (when mentioned in the marketing authorization application)	Conditions to be fulfilled	Documents and data	Procedure
a) Deletion of a manufacturer	1	1	IA
b) Replacement or addition of a manufacturer	1, 2, 3, 4	1, 2, 3	IA
c) Any change to manufacturers of spacer devices for metered dose inhalers	–	–	II
d) Change in the name of a manufacturer of a component of the packaging (closure) system (primary packaging) <*>	5	1	IA

Conditions 1. No deletion of any packaging component or device. 2. The qualitative and/or quantitative composition of materials of components of the packaging (closure) system (primary packaging) or additional products (including devices and component parts), as well as design specifications remain the same. 3. The specifications and quality control methods are at least equivalent. 4. The sterilization method and conditions remain the same, if applicable. 5. There is no change in a manufacturer of a component of the packaging (closure) system (primary packaging) or additional products (including devices and component parts).
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application. 2. Documents and information on the medical product that are attached to the medicinal product in accordance with paragraph 187 of these Rules. 3. Comparative table of current and proposed specifications, if applicable.

<*> Note	If necessary, this information is subject to deletion from the marketing authorization application for the medicinal product.

B.II.d.8. Addition or change of the calendar packaging for an already authorized pack size of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
	1	1, 2, 3, 4, 5	IAIN

Conditions 1. The primary packaging material remains the same; the functional characteristics (protective properties) of the material remain the same.
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application. 2. Necessary data on the new packaging. 3. Comparison of current and proposed primary packaging specifications, if applicable. 4. As appropriate, drawings of a new container (closure). 5. Proof that the pack size is consistent with the dosage regimen and duration of treatment and adequate for the dosing instructions as approved in the summary of product characteristics. ”;

B.II.f) Stability

B.II.f.1. Change in the shelf life or storage conditions of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure

a) Reduction of the shelf life of the medicinal product			
1. As packaged in secondary packaging	1	1, 2, 3	IA_{IN}
2. After the 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 medicinal product			
1. As packaged in secondary packaging (supported by real-time data)	-	1, 2, 3	IB
2. After the 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 acts of the Union's governing bodies in the field of medicines circulation <*>	-	-	II
5. Extension of the shelf life of a biological 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 medicinal 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 of a stability change. 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 marketing authorization application. This must contain results of appropriate real-time stability studies (covering the entire shelf life) conducted in accordance with the acts of the Union's governing bodies in the field of medicines circulation on at least two pilot scale batches <1> of the medicinal product in the authorized packaging material and/or after the first opening or reconstitution, as appropriate; where applicable, results of appropriate microbiological testing should be included. 2. Revised medicinal product information. 3. Copies of approved end-of-shelf life specifications and, where applicable, specifications after dilution/reconstitution or the first opening (in the form of a link to the relevant document in the dossier sequence or an annex to the cover letter). 4. Justification for the proposed changes.

<*> Note	Extrapolation not applicable for a biological medicinal product.
<1>	Pilot batches can be accepted with a commitment to verify the shelf life on production batches.

B.II.g) Design space and post-approval change management protocols

B.II.g.1. Introduction of a new design space or extension of an approved design space for the medicinal product, concerning:	Conditions to be fulfilled	Documents and data	Procedure
a) One or more unit operations in the manufacturing process of the medicinal product, including the resulting in-process controls and/or analytical procedures	–	1, 2, 3	II
b) Analytical procedures for excipients/intermediates and/or the medicinal 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, process parameters and the critical quality attributes of the medicinal 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 marketing authorization application.

B.II.g.2. Introduction of a post-approval change management protocol related to the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
	–	1, 2, 3	II

Documentation
1. Detailed description for the proposed change.
2. Change management protocol related to the medicinal product.
3. Amendment of the relevant section(s) of the marketing authorization application.

B.II.g.3. Deletion of an approved change management protocol related to the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
	1	1, 2	IA_{IN}

Conditions
1. The deletion of the approved change management protocol related to the medicinal 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 marketing authorization application.

Documentation
1. Justification for the proposed deletion.
2. Amendment of the relevant section(s) of the marketing authorization application.

B.II.g.4. Changes to an approved change management protocol	Conditions to be fulfilled	Documents and data	Procedure
a) Major changes to an approved change management protocol	–	–	II
b) Minor changes to an approved	–	1	IB

change management protocol that do not change the strategy defined in the protocol			
Documentation 1. Proof from the marketing authorization holder that any change should be within the range of currently approved acceptance criteria. In addition, proof that an assessment of comparability is not required for biological medicinal products.			
B.II.g.5. Implementation of changes provided for in an approved change management protocol	Conditions to be fulfilled	Documents and data	Procedure
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 medicinal product	-	1, 2, 3, 4, 5	IB
Conditions 1. The proposed change has been performed fully in accordance with the approved change management protocol, which requires immediate notification following implementation.			
Documentation 1. Reference to the approved change management protocol. 2. Proof from the marketing authorization holder that the change is in accordance with the approved change management protocol and that the study results meet the acceptance criteria specified in the protocol. In addition, proof that an assessment of comparability is not required for biological 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 marketing authorization application. 5. Copies of approved specifications of the medicinal product (in the form of a link to the relevant document in the dossier sequence or an annex to the cover letter).			

B.II.h) Adventitious agents safety

B.II.h.1. Update to the information "Adventitious Agents	Conditions to be fulfilled	Documents and data	Procedure

Safety Evaluation (name, dosage form, manufacturer)" (Section 3.2.A.2 of the marketing authorization application)			
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 marketing authorization application			
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 marketing authorization application, including the introduction of the new studies to investigate the capability of manufacturing steps to inactivate/eliminate adventitious agents. 2. Justification that the studies do not modify the risk assessment. 3. Amendment of product information (where applicable).			

B.III. Certificate of Suitability to the European Pharmacopoeia (CEP) (if any) and/or TSE Certificate of Suitability and/or changes in the active pharmaceutical ingredient and excipients to comply with the Pharmacopoeia of the Union, the pharmacopoeia of a Member State or other pharmacopoeias in accordance with the Concept

B.III.1. Submission of a new or updated Ph. Eur. Certificate of Suitability or deletion of a Ph. Eur. Certificate of Suitability for: an active pharmaceutical ingredient; a starting material/reagent/ intermediate used in the manufacturing process of the active pharmaceutical ingredient; an excipient.	Conditions to be fulfilled	Documents and data	Procedure
a) Certificate of Suitability to the			

European Pharmacopoeia			
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 pharmaceutical ingredient 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) Ph. Eur. TSE Certificate of Suitability for an active pharmaceutical ingredient/starting material/reagent/intermediate/ excipient			
1. New certificate for an active pharmaceutical ingredient 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/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	–	–	II

which an assessment of the risk with respect to potential contamination with adventitious agents is required			

Conditions

1. Medicinal product release and end-of-shelf life specifications remain the same.
2. Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with the guidelines of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) and product specific requirements (e.g. particle size profiles, polymorphic forms), if applicable.
3. The manufacturing process of the active pharmaceutical ingredient, 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 an active pharmaceutical ingredient 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 pharmaceutical ingredient/starting material/reagent/ intermediate/excipient is not sterile.
6. For herbal preparations: the manufacturing route, physical form, extraction solvent and drug extract ratio should remain the same.
7. If gelatine manufactured from bones is to be used in a medicinal product for parenteral use, it should only be manufactured in accordance with the requirements of the manufacturer's country.
8. At least one manufacturer for the same substance remains in the marketing authorization application.
9. If the active pharmaceutical ingredient is a not a sterile substance but is to be used in a sterile medicinal product, then in accordance with the CEP it must not use water during the last steps of the synthesis or, if it does, the active pharmaceutical ingredient 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 and additionally the cover letter should clearly outline the present and proposed manufacturers.
3. Amendment of the relevant section(s) of the marketing authorization application.
4. Where applicable, a document providing information of any materials falling within the scope of the monograph of the Pharmacopoeia of the Union or the European Pharmacopoeia on minimizing 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 pharmaceutical ingredient/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. For an active pharmaceutical ingredient, a declaration by the qualified person of each of the manufacturing authorization holders listed in the application where the active pharmaceutical ingredient is used as a starting material and a declaration by the qualified person of each of the manufacturing authorization holders listed in the application as responsible for batch release. These declarations should state that the active pharmaceutical ingredient manufacturer referred to in the application carries out its activities in accordance with the Rules of Good Manufacturing Practice for starting materials. A single declaration may be acceptable under certain circumstances (see the note under variation B.II.b.1). The manufacture of intermediates also requires a declaration by the qualified person, while as far as any updates to certificates for active pharmaceutical ingredients and intermediates are concerned, a declaration by the qualified person 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 pharmaceutical ingredient with the corresponding requirements on quality of water for pharmaceutical use.

B.III.2. Changes in the active pharmaceutical ingredient or an excipient to comply with the Pharmacopoeia of the Union, the pharmacopoeia of a Member State or other pharmacopoeias in accordance with the Concept	Conditions to be fulfilled	Documents and data	Procedure
a) Change of specification(s) of a former non-pharmacopoeial substance to fully comply with the Pharmacopoeia of the Union or with the pharmacopoeia of a			

Member State			
1. Active pharmaceutical ingredient	1, 2, 3, 4, 5	1, 2, 3, 4	IA_{IN}
2. Excipient/active pharmaceutical ingredient starting material	1, 2, 4	1, 2, 3, 4	IA
b) Changes to comply with an update of the relevant monograph of the Pharmacopoeia of the Union, the pharmacopoeia of a Member State or other pharmacopoeias in accordance with the Concept	1, 2, 4, 5	1, 2, 3, 4	IA
c) Change in specifications from the pharmacopoeia of a Member State to the Pharmacopoeia of the Union	1, 4, 5	1, 2, 3, 4	IA
d) Change to replace the manufacturer's test procedure with the procedures of the Pharmacopoeia of the Union, the pharmacopoeia of a Member State and/or other pharmacopoeias according to the Concept in relation to the active pharmaceutical ingredient, an excipient, starting material and/or primary packaging material		1, 2, 3, 4	IA
e) Change in the classification of an excipient from a "novel excipient" (3.2.P.4.6) to an "excipient according to the Pharmacopoeia of the Union and/or other pharmacopoeias according to the Concept" (3.2.P.4.1)	6, 7, 8, 9, 10	1, 2	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, the polymorphic form or, e.g. bioassays, aggregates). 3. No significant changes in the qualitative and quantitative impurity profile unless the specifications are tightened. 4. Additional validation of a new or changed pharmacopoeial procedure is not required. 5. For herbal preparations: the manufacturing route, physical form, extraction solvent and drug extract ratio should remain the same. 6. An excipient fully complies with the requirements of the monograph in the relevant pharmacopoeia, and all tests comply with pharmacopoeial standards. 7. Additional specification parameters for specific properties are unchanged (e.g. particle size distribution, the polymorphic form or, e.g. bioassays, aggregates). 8. An excipient must remain unchanged. 9. Additional validation of a new or changed pharmacopoeial method is not required. 10. An excipient has already been approved by the authorized authority for use in the medicinal product with a specific route of administration.	
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application. 2. Comparative table of current and proposed specifications. 3. Batch analysis data (in a comparative tabulated format) on at least two production batches of the relevant substance for all tests in the new specification and additionally, where appropriate, comparative dissolution profile data for the medicinal product on at least one pilot batch. For herbal medicinal products, comparative disintegration data may be sufficient. 4. Data to demonstrate the suitability of the monograph to control the substance, e.g. a comparison of the potential impurities with other specified and detectable impurities in the API, a starting material or an excipient.	
Note:	There is no need to notify the authorized authorities of an updated monograph of the Pharmacopoeia of the Union or the pharmacopoeia of a Member State in the case that a specification is introduced under the relevant updated monograph within six months after its publication and reference is made to the “current edition (in accordance with the legislation of a Member State)” in the marketing authorization application for an authorized medicinal product.

B.IV. Medical products (devices and component parts) included in the packaging of the medicinal product

B.IV.1. Change of component parts for measuring, including medical products for administration	Conditions to be fulfilled	Documents and data	Procedure
a) Addition or replacement of devices or component parts, including medical products, which are not an integrated part of the primary packaging			
1. Medical products authorized in accordance with the Rules of Marketing Authorization and Assessment of the Safety, Quality and Efficiency of Medical Products approved by Decision No. 46 of the Eurasian Economic Commission's Council dated February 12, 2016, or in accordance with the legislation of a Member State or authorized for circulation in third countries	1, 2, 3, 5, 6	1, 2, 3	IA_{IN}
2. Medical products (devices and component parts) which may have a significant impact on the delivery of the active substance in the medicinal product (e.g. spacer devices for metered dose inhalers, nebulizers)	–	–	II
b) Deletion or replacement of medical products (devices and component parts) included in the packaging of the medicinal product	4	1, 4	IA_{IN}
c) Addition or replacement of a device or component part which is an integrated part of the primary packaging	–	–	II

Conditions 1. The proposed measuring/administration device must accurately deliver the required dose for the product concerned in line with the approved posology. Results of such studies should be available. 2. The new measuring/administration device is compatible with the medicinal product. 3. The change should not lead to substantial amendments of product information. 4. The medicinal product can still be accurately delivered. 5. The medical product is not used as a solvent of the medicinal product. 6. If the function of accurate measurement is intended, the information on it should be included in the marketing authorization application for the medicinal product.
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application, including the scheme of the component part/medical product, the composition of its materials, the information on the supplier where appropriate, and revised product information as appropriate. 2. Document confirming the marketing authorization of a medical product in the Union or in accordance with the legislation of a Member State or authorization for circulation in third countries (if applicable). 3. Documents and information to demonstrate dosing accuracy and compatibility of the component part or the medical product with the medicinal product. 4. Justification for the deletion or replacement of the medical product (device or component part).

Note:	For B.IV.1.c), any change which results in a new dosage form requires the submission of an extension application.

B.V. Changes to a marketing authorization application 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 application for a medicinal product (PMF 2nd step procedure)	Conditions to be fulfilled	Documents and data	Procedure
a) First-time inclusion of a new Plasma Master File affecting the properties of the medicinal product	-	-	II
b) First-time inclusion of a new Plasma Master File not affecting the properties of the medicinal	-	1, 2, 3, 4	IB

product			
c) Inclusion of an updated/amended Plasma Master File when changes affect the properties of the medicinal product	-	1, 2, 3, 4	IB
d) Inclusion of an updated/amended Plasma Master File when changes do not affect the properties of the medicinal product	1	1, 2, 3, 4	IA_{IN}
Conditions 1. The updated or amended PMF has been granted the PMF certificate of the Union in accordance with Appendix 1 to the Rules of Marketing Authorization and Assessment.			
Documentation 1. Proof that the PMF certificate of the Union and the assessment report are fully applicable for the authorized product. The PMF holder has provided the PMF certificate of the Union, the assessment report and the PMF dossier to the marketing authorization holder (where the marketing authorization holder is different from the PMF holder). The PMF certificate of the Union and the assessment report replace the previous PMF documentation for this medicinal product. 2. PMF certificate of the Union and assessment report. 3. A declaration by the qualified person that outlines all the changes introduced with the certified PMF and evaluates their potential impact on the medicinal products, including product specific risk assessments. 4. The variation application form should clearly reflect the present and proposed PMF certificate of the Union (code number) in the marketing authorization application. When applicable, the variation application form should clearly list also all the other PMFs to which references are made in the marketing authorization application for the medicinal product even if these PMFs 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 application for a medicinal product (VAMF 2nd step procedure)	Conditions to be fulfilled	Documents and data	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 medicinal 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 medicinal product	1	1, 2, 3, 4	IA_{IN}
Conditions 1. The updated or amended VAMF has been granted the VAMF certificate of the Union in accordance with Appendix 1 to the Rules of Marketing Authorization and Assessment.			
Documentation 1. A declaration that the VAMF certificate of the Union and the assessment report are fully applicable for the authorized product. The VAMF holder has provided the VAMF certificate of the Union, the assessment report and the VAMF dossier to the marketing authorization holder (where the marketing authorization holder is different from the VAMF holder). The VAMF certificate of the Union and the assessment report replace the previous VAMF documentation for this medicinal product. 2. VAMF certificate of the Union and assessment report. 3. A declaration by the qualified person that outlines all the changes introduced with the certified VAMF and evaluates their potential impact on the medicinal products, including product specific risk assessments. 4. The variation application form should clearly reflect the present and proposed VAMF certificate of the Union (code number) in the marketing authorization application. When applicable, the variation application form should clearly list also all the other VAMFs to which references are made in the marketing authorization application for the medicinal product even if these VAMFs are not the subject of the application.			

B.V.b) Updates as a result of requests from authorized authorities (expert organizations), including based on the results of consideration by the Expert Committee

B.V.b.1. Update of the quality dossier intended to implement the opinion or request of the authorized authority (expert organization) (recommendation of the Expert Committee)	Conditions to be fulfilled	Documents and data	Procedure
a) The change implements the	1	1, 2	IA_{IN}

opinion or request of the authorized authority (expert organization) (recommendation of the Expert Committee)			
b) The harmonization of the quality dossier was not part of the opinion or request of the authorized authority (expert organization) (recommendation of the Expert Committee), 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 opinion or request of the authorized authority (expert organization) (recommendation of the Expert Committee). 2. The changes introduced during the procedure of referral to the authorized authority (expert organization) should be clearly highlighted in the submission.			

”;

c) in Section C of the table:

Subsections C.I.1–C.I.8 shall read as follows:

“C.I. Human medicinal products

C.I.1. Change(s) in the summary of product characteristics, packaging mock-ups or the package leaflet intended to implement the requirements specified in the opinion or request of the authorized authority (expert organization)	Conditions to be fulfilled	Documents and data	Procedure
a) The marketing authorization application for the medicinal product is undergoing assessment by the authorized authority (expert organization)	1	1, 2, 3	IA_{IN}
b) The marketing authorization application for the medicinal product has not been filed for assessment with the authorized authority (expert organization)	1	1, 2, 3	IA

but changes implement the requirements specified in the opinion or request of the authorized authority (expert organization) and no new additional data is required to be submitted by the marketing authorization holder			
c) Changes implement the requirements specified in the opinion or request of the authorized authority (expert organization) with new additional data submitted by the marketing authorization holder	-	-	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 opinion or request of the authorized authority (expert organization) with the annexed summary of product characteristics, packaging mock-ups or package leaflet. 2. A declaration that the proposed summary of product characteristics, packaging mock-ups and package leaflet are identical in the concerned sections to those annexed to the opinion or request of the authorized authority (expert organization). 3. Revised medicinal product information.			
C.I.2. Change(s) in the summary of product characteristics, packaging mock-ups or the package leaflet of a generic, hybrid or biosimilar medicinal product following assessment of the same change for the reference medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Implementation of change(s) for which no new additional data is required to be submitted by the marketing authorization holder	–	1, 2	IB
b) Implementation of change(s) which require to be further substantiated by new additional	–	–	II

data to be submitted by the marketing authorization holder (e.g. comparability)			
Documentation 1. Attached to the cover letter of the variation application: A request of the authorized authority, if applicable. 2. Revised medicinal product information.			
C.I.3. Change(s) in the summary of product characteristics, packaging mock-ups or the package leaflet of human medicinal products intended to implement the outcome of a post-authorization safety study or the conclusion and proposed follow-up actions in a periodic safety update report	Conditions to be fulfilled	Documents and data	Procedure
a) Implementation of wording agreed by the authorized 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 marketing authorization holder	–	–	II
Conditions 1. The variation introduces the wording agreed by the authorized 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 agreement/assessment of the authorized authority. 2. Revised medicinal product information.			
C.I.4. Significant change(s) in the summary of product characteristics because of new quality, preclinical, clinical or pharmacovigilance data	Conditions to be fulfilled	Documents and data	Procedure
	–	–	II
Note:	This variation does not apply when the new data has been submitted in accordance with variation C.I.13. In such cases,		

	the change in the summary of product characteristics, packaging mock-ups and/or the package leaflet is classified as variation C.I.13.

C.I.5. Change in the legal status of a medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) For generic, hybrid or 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 the legal status change of the reference medicinal product (e.g. reference to the decision adopted by the authorized authority of a Member State).
2. Revised medicinal product information.

C.I.6. Change(s) to the therapeutic indication(s) and/or dosage regimen	Conditions to be fulfilled	Documents and data	Procedure
a) Addition of a new therapeutic indication and/or dosage regimen or modification of the approved ones	–	–	II
b) Deletion of a therapeutic indication and/or dosage regimen	–	–	IB

Note	Where the addition or modification of a therapeutic indication and/or dosage regimen takes place in the context of the implementation of the requirements specified in the opinion or request of the authorized authority (expert organization), or – for a generic, hybrid or biosimilar product – when the changes of product information have been made following the assessment of similar changes for the reference medicinal product, such changes are classified as variations C.I.1 and C.I.2, respectively.

C.I.7 Deletion of:	Conditions to be fulfilled	Documents and data	Procedure
a) dosage form	–	1, 2	IB
b) a strength	–	1, 2	IB

Documentation 1. A declaration that the remaining product presentation(s) is (are) adequate for the dosing instructions and treatment duration as described in the summary of product characteristics. 2. Revised medicinal product information.			
Note	In cases where a given dosage form or strength has received a marketing authorization as a separate medicinal product, the deletion of such dosage form or strength will not be a variation but the withdrawal of the marketing authorization.		
C.I.8. Introduction of, or changes to, a summary of the pharmacovigilance system of the marketing authorization holder for the medicinal product for human use <*>	Conditions to be fulfilled	Documents and data	Procedure
a) Introduction of a summary of the pharmacovigilance system of the marketing authorization holder for the medicinal product, changes in the qualified person responsible for pharmacovigilance (QPPV) (including contact information) and/or changes in the Pharmacovigilance System Master File (PSMF) location	-	1, 2	IA_{IN}
Documentation 1. Summary of the pharmacovigilance system of the marketing authorization holder for the medicinal product or update of the relevant elements (as applicable): proof that the applicant has at disposal a QPPV and a statement signed by the applicant to the effect that the applicant has the necessary means to fulfill the tasks and responsibilities listed in the Rules of Good Pharmacovigilance Practice; contact information of the QPPV, the Member State in which the QPPV resides and carries out his/her tasks; PSMF location. 2. PSMF number (if available).			

Subsection C.I.9 shall be invalidated;

Subsections C.I.10–C.I.13 shall read as follows:

“

C.I.10. Change in the frequency and/or date of submission of	Conditions to be fulfilled	Documents and data	Procedure

periodic safety update reports (PSUR) for medicinal products			
	1	1, 2	IA_{IN}
Conditions 1. The change in the frequency and/or date of submission of the periodic safety update report has been agreed by the authorized authority of a Member State.			
Documentation 1. Attached to the cover letter of the variation application: A reference to the agreement of the authorized authority. 2. Revised frequency and/or date of submission of the periodic safety update report.			
Note	This variation applies only when the submission frequency of periodic safety update reports is specified in the marketing authorization application by other means than a reference to the list of reference dates in accordance with the acts of the Union's governing bodies in the field of medicines circulation and where the submission of a periodic safety update report 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	Documents and data	Procedure
a) Implementation of wording agreed by the authorized 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 marketing authorization holder where significant assessment by the authorized authority is required <*>	–	–	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 authorized authority. 2. Revised medicinal product information.			

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 in exceptional cases and conditional marketing authorization.
<*>	The introduction of a risk management plan requested by the authorized authority always requires significant assessment.

C.I.12. Inclusion or deletion of the black triangle symbol or explanatory statements for medicinal products that are subject to additional monitoring in accordance with the recommendation of the Expert Committee	Conditions to be fulfilled	Documents and data	Procedure
	1	1, 2	IA_{IN}

Conditions
1. The medicinal product is subject to additional monitoring in accordance with the recommendation of the Expert Committee.

Documentation
1. Attached to the cover letter of the variation application: A reference to the recommendation of the Expert Committee.
2. Revised medicinal product information.

Note	This variation covers the situation where the inclusion or deletion of the black triangle symbol or explanatory statements is not performed as part of another regulatory procedure (e.g. the procedure of confirmation (renewal) of the marketing authorization or the variation procedure affecting product information).

C.I.13. Other variations not specifically covered elsewhere in this Annex which involve the submission of clinical trials to the authorized authority <*>	Conditions to be fulfilled	Documents and data	Procedure
	–	–	II

Note	In cases where the assessment by the authorized authority of the data submitted leads to a change of the summary of product characteristics, packaging mock-ups or the package leaflet, the relevant amendment to the summary of product characteristics, packaging mock-ups or the package leaflet is covered by the variation.

<*>	This variation does not apply to variations that can be considered as Type IB by default in accordance with any other section of this Annex.

”;

the following Subsection C.I.14 shall be added:

“

B.I.14. Clarification of storage conditions during the use of the medicinal product in Section 4.2 of the summary of product characteristics and Section 3 of the package leaflet to ensure proper handling of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
	–	1, 2, 3	IB
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application. The amendment must contain results of appropriate real-time stability studies (covering the entire shelf life, if applicable) conducted in accordance with the acts of the Union’s governing bodies in the field of medicines circulation on at least one pilot scale batch of the medicinal product in the authorized packaging material and/or after the first opening or reconstitution, as appropriate. Where applicable, results of appropriate microbiological testing should be included. 2. Revised medicinal product information. 3. Copies of approved end-of-shelf life specifications and, where applicable, specifications after dilution/reconstitution or the first opening (in the form of a link to the relevant document in the dossier sequence or an annex to the cover letter).			

”;

d) Section D of the table shall read as follows:

“D. PMF/VAMF

D.1. Change in the name and/or address of the VAMF certificate holder	Conditions to be fulfilled	Documents and data	Procedure
	1	1	IA_{IN}
Conditions 1. The VAMF certificate holder must remain the same juridical person.			
Documentation 1. A formal document from a relevant authorized authority (e.g. a tax authority) 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	Documents and data	Procedure
	1	1	IA_{IN}
Conditions 1. The PMF certificate holder must remain the same juridical person.			
Documentation 1. A formal document from a relevant authorized authority (e.g. a tax authority) 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. a different juridical person	Conditions to be fulfilled	Documents and data	Procedure
	-	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 transaction date – signed by both companies. 2. Copy of the last page in the PMF certificate of the Union. 3. Proof of establishment of the new holder (Excerpt from the register of juridical persons 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 information of the person responsible for communication between the authorized authority and the PMF holder, signed by the transferee. 6. Letter of Undertaking to fulfill 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	Documents and data	Procedure
	1, 2	1, 2, 3	IA
Conditions 1. The blood establishment must remain the same juridical person. 2. The change must be administrative (e.g. merger, take-over); in case of the change in the name of the blood establishment (blood/plasma collection center), its organizational and legal form of ownership, as well as location must remain the same.			

Documentation 1. A signed declaration that the change does not involve a change of the quality system within the blood establishment. 2. A signed declaration that there is no change in the list of the blood/plasma 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	Documents and data	Procedure
	-	1, 2, 3	IB
Documentation 1. Epidemiological data for viral markers related to the blood/plasma collection center covering the last three years. For a newly opened blood/plasma collection center(s) or if no data is yet available, proof that epidemiological data will be provided at the time of the next annual update(s). 2. A statement that the blood/plasma collection center is working under the same conditions as the other centers belonging to the blood establishment, as specified in the standard agreement between the blood establishment and the PMF holder. 3. Updated relevant sections and annexes of the PMF dossier.			
D.6. Deletion or change of status (operational/non-operational) of blood establishments (blood/plasma collection centers) used for blood/plasma collection or in the testing of donations and plasma pools	Conditions to be fulfilled	Documents and data	Procedure
	1, 2	1	IA
Conditions 1. The reason for deletion or change of status should not be related to non-compliance with the requirements of the Rules of Good Manufacturing Practice. 2. The blood establishments (blood/plasma collection centers) should comply with the acts of the Union's governing bodies in the field of pharmaceutical inspections and the legislation of the Member State to the extent not regulated by the acts of the Union's governing bodies 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	Conditions to be	Documents	Procedure

establishment for the collection of blood/plasma not included in the PMF	fulfilled	and data	
	-	-	II
D.8. Replacement or addition of a blood/plasma collection center for testing of donations and/or plasma pools within a blood establishment already included in the PMF	Conditions to be fulfilled	Documents and data	Procedure
	-	1, 2	IB
Documentation 1. A statement that the testing is performed following the same standard operating procedures 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	Documents and data	Procedure
	–	–	II
D.10. Replacement or addition of a new blood establishment or center in which storage of plasma is carried out	Conditions to be fulfilled	Documents and data	Procedure
	–	1, 2	IB
Documentation 1. A statement that the plasma storage center is working in accordance with the same standard operating procedures as the already accepted blood establishment. 2. Updated relevant sections and annexes of the PMF dossier.			
D.11. Deletion of a blood establishment or center in which storage of plasma is carried out	Conditions to be fulfilled	Documents and data	Procedure
	1	1	IA
Condition 1. The reason for deletion should not be related to non-compliance with the requirements of the Rules of Good Manufacturing Practice.			

Documentation 1. Updated relevant sections and annexes of the PMF dossier.			
D.12. Replacement or addition of an organization involved in the transportation of plasma	Conditions to be fulfilled	Documents and data	Procedure
	–	1	IB
Documentation 1. Updated relevant sections and annexes of the PMF dossier, including all the blood establishments using this transportation organization, a summary of the system in place to ensure that the transportation is performed under appropriate conditions (time, temperature and compliance with the Rules of Good Manufacturing Practice) and confirmation that transportation conditions are validated.			
D.13. Deletion of an organization involved in the transportation of plasma	Conditions to be fulfilled	Documents and data	Procedure
	1	1	IA
Condition 1. The reason for deletion should not be related to non-compliance with the Rules of Good Manufacturing Practice.			
Documentation 1. Updated relevant sections and annexes of the PMF dossier.			
D.14. Addition of a test kit authorized in the Union as a medical product to test individual blood and plasma donations as a new test kit	Conditions to be fulfilled	Documents and data	Procedure
	1	1, 2	IA
Conditions 1. The new test kit is authorized in the Union as a medical product.			
Documentation 1. A list of testing sites where the kit is used. 2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing in accordance with the acts of the Union's governing bodies in the field of medicines circulation.			
D.15. Addition of a test kit not authorized in the Union as a medical product to test individual	Conditions to be fulfilled	Documents and data	Procedure

blood and plasma donations as a new test kit			
a) The new test kit has not previously been approved in the PMF for any blood/plasma collection center for testing of donations	-	-	II
b) The new test kit has been approved in the PMF for other blood/plasma collection centers for testing of donations	-	1, 2	IA
Documentation 1. A list of testing centers where the kit is currently used and a list of testing centers where the kit will be used. 2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing in accordance with the acts of the Union's governing bodies in the field of medicines circulation.			
D.16. Change of the kit/method used to test pools (antibody or antigen or Nucleic Acid Amplification Technology test)	Conditions to be fulfilled	Documents and data	Procedure
	–	–	II
D.17. Introduction or extension of the quarantine storage procedure	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA
Condition 1. The quarantine storage procedure is a more stringent procedure (e.g. release only after retesting of donors).			
Documentation 1. Updated relevant sections and annexes of the PMF dossier, including the rationale for introduction or extension of the quarantine storage procedure, the sites where quarantine storage takes place and, for changes to the procedure, a decision tree including new conditions.			
D.18. Removal of the quarantine storage period or reduction in its length	Conditions to be fulfilled	Documents and data	Procedure
	-	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	Documents and data	Procedure
a) The new blood containers are authorized in the Union as medical products	1, 2	1	IA
b) The new blood containers are not authorized in the Union as medical products	-	-	II
Conditions 1. The container is authorized in the Union as a medical product. 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 the container, manufacturer, anticoagulant solution specification, confirmation of marketing authorization in the Union or a Member State and the name of the blood establishments where the container is used.			
D.20. Change in storage/transportation	Conditions to be fulfilled	Documents and data	Procedure
a) storage and/or transportation 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 the requirements of the Pharmacopoeia of the Union or otherwise the pharmacopoeias of the Member States 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 a detailed description of the new conditions, confirmation of validation of storage/transportation conditions and the name of the blood establishment where the change takes place (if relevant).			
D.21. Introduction of a test for viral markers when this introduction will have a significant impact on the viral	Conditions to be fulfilled	Documents and data	Procedure

risk assessment			
	-	-	II
D.22. Change in the plasma pool preparation (e.g. the manufacturing method, pool size, storage of plasma pool samples)	Conditions to be fulfilled	Documents and data	Procedure
	-	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	Documents and data	Procedure
	–	–	II

B) in Annex VI:

Subsections A.1–A.7 shall read as follows:

"A. Administrative changes

A.1. Change of marketing authorization holder	Conditions to be fulfilled	Documents and data	Procedure
a) Change of name and/or address of the marketing authorization holder	1	1, 3	IA_{IN}
b) Transfer of marketing authorization certificate from one marketing authorization holder to another juridical person	2	1, 2, 3, 4	IA_{IN}
Conditions 1. The marketing authorization holder must remain the same juridical person. 2. The marketing authorization holder is another juridical person.			
Documentation 1. A copy of the document issued by the relevant authorized authority of the country of registration of the juridical person being the marketing authorization holder (e.g. a tax authority) that specifies the name and/or address of the new marketing authorization holder or the new name and/or			

address of the marketing authorization holder.
2. Documents justifying the transfer of the marketing authorization certificate(s) and confirming the ability of the new marketing authorization holder to ensure the proper performance of all the marketing authorization holder's obligations;
copy of the document confirming the transfer of the marketing authorization certificate from one juridical person to another;
revised pharmacovigilance summary or revised pharmacovigilance system master file, if included in the marketing authorization application;
information about the organization responsible for handling complaints in the Eurasian Economic Union.
3. Medicinal product information revised in the relevant sections.
4. Document(s) submitted by the juridical person to which the powers of the marketing authorization holder are transferred, confirming the absence of changes in medicinal product information that are not related to the transfer of the marketing authorization.

A.2. Change in the (brand) name of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) medicinal products authorized in accordance with the Rules of Marketing Authorization and Assessment	1	1, 2	IAIN
b) medicinal products authorized only in the reference Member State, including in accordance with the legislation of the Member State	–	1, 2	IB

Conditions
1. The check by the authorized authority (expert organization) of the reference Member State on the acceptability of the new (brand) name has been finalized and was positive.

Documentation
1. Justification of the applicant for the acceptability of the new (brand) name.
2. Revised medicinal product information.

A.3. Change in name of the active pharmaceutical ingredient or of an excipient	Conditions to be fulfilled	Documents and data	Procedure
	1	1, 2	IA_{IN}

Conditions
1. The active pharmaceutical ingredient/excipient must remain the same.

Documentation
1. Justification for the WHO to change the name of the active pharmaceutical

ingredient. For an excipient: justification for amending the Union's directory (classifier) of excipients. Proof that the change is in line with the Pharmacopoeia of the Union (if applicable) or otherwise with a Pharmacopoeia of a Member State. A declaration that the name of the herbal medicinal product is in accordance with the acts of the Union's governing bodies in the field of medicines circulation. 2. Revised medicinal product information.			
A.4. Change in the name and/or address of: a manufacturer (including, where relevant, quality control testing sites); or an APIMF holder; or a supplier of the active pharmaceutical ingredient, starting material, reagent, or intermediate used in the manufacture of the active pharmaceutical ingredient (where specified in the marketing authorization application) where no Ph. Eur. Certificate of Suitability is part of the approved marketing authorization application; or a manufacturer of a novel excipient (where specified in the marketing authorization application)	Conditions to be fulfilled	Documents and data	Procedure
	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 authorized authority (e.g. a tax authority) in which the new name and/or address is mentioned. 2. Amendment of the relevant section(s) of the marketing authorization application. 3. In case of change in the name of the active pharmaceutical ingredient master file (APIMF) holder, updated letter of access.			
A.5. Change in the name and/or address of a manufacturer/importer of the medicinal product (including batch release or quality control testing sites)	Conditions to be fulfilled	Documents and data	Procedure

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 manufacturing license, if available; or a formal document from a relevant authorized authority (e.g. a tax authority) in which the new name and/or address is mentioned. 2. If applicable, amendment of the relevant section(s) of the marketing authorization application, including revised medicinal product information as appropriate.			
A.6. Change in ATC Code	Conditions to be fulfilled	Documents and data	Procedure
a) Change following approval of or amendment to ATC Code by the WHO	1	1	IA
b) Change at the applicant's initiative of a code other than the code assigned by the WHO	–	1	IB
Conditions 1. Change following approval of or amendment to ATC Code by the WHO.			
Documentation 1. Revised medicinal product information.			
A.7. Deletion of manufacturing sites for an active pharmaceutical ingredient, intermediate or medicinal product, a packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the marketing authorization application)	Conditions to be fulfilled	Documents and data	Procedure

	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. 2. The deletion should not be due to critical deficiencies concerning manufacturing.			
Documentation 1. The paragraph of the variation application form on changes should clearly outline the previously approved and proposed manufacturers as listed in Section 2 of the application form. 2. Amendment of the relevant section(s) of the marketing authorization application, including revised medicinal product information as appropriate.			

”;

Subsection A.8 shall be invalidated;

c) Section B of the table shall read as follows:

“B. Quality changes

B.I. Active pharmaceutical ingredient

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 pharmaceutical ingredient or change in the active pharmaceutical ingredient manufacturer (including, where relevant, quality control testing sites), where no Ph. Eur. Certificate of Suitability is part of the approved marketing authorization application	Conditions to be fulfilled	Documents and data	Procedure
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, 9	IA_{IN}
b) Introduction of a manufacturer of the active pharmaceutical ingredient	–	–	II

supported by an APIMF <*>			
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 pharmaceutical ingredient, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting bioavailability <*>	–	–	II
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 pharmaceutical ingredient or a starting material/reagent/intermediate used in the manufacture of a biological medicinal product	–	–	II
f) Changes to quality control testing arrangements for the active pharmaceutical ingredient – 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 pharmaceutical ingredient that is not supported by an APIMF and requires significant update to Section 3.2.S of the marketing authorization application for the medicinal product <*>	–	–	II
h) Addition of an alternative sterilization site for the active pharmaceutical ingredient	–	1, 2, 4, 5, 8	IB

using a method of the Pharmacopoeia of the Union or otherwise the methods of other pharmacopoeias in accordance with the Concept for Harmonizing the Pharmacopoeias of the Eurasian Economic Union Member States approved by Decision No. 119 of the Eurasian Economic Commission's Board dated September 22, 2015 (hereinafter referred to as the Concept)			
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 Bank	–	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 pharmaceutical ingredients, the specifications (including in-process controls, methods of analysis of all materials), method of preparation (including the batch size) and detailed route of synthesis are identical to those already approved.
2. The active pharmaceutical ingredient is not a biological substance or sterile.
3. Materials of human or animal origin are used in the process and the active pharmaceutical ingredient manufacturer:
   does not use any new supplier for which assessment is required of viral safety or of compliance with the Pharmacopoeia of the Union and Chapter 24 of the Rules of Biological Medicinal Products Research on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products;
   uses a new supplier for which such assessment has been performed.

4. Method transfer from the old to the new site has been successfully completed.
5. The particle size specification of the active pharmaceutical ingredient and the corresponding analytical method remain the same.

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application, if applicable.
2. Proof from the marketing authorization holder or the APIMF 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 preparation and manufacturing route) quality control procedures and specifications of the active pharmaceutical ingredient and of the starting material/reagent/intermediate in the manufacturing process of the active pharmaceutical ingredient (if applicable) are the same as those already approved.
3. 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 authorized authority and shown to comply with the Pharmacopoeia of the Union and Chapter 24 of the Rules of Biological Medicinal Products Research on minimizing the risk of transmitting the animal spongiform encephalopathy agents via human and veterinary medicinal products. Such documentary evidence should include the following information: name of manufacturer, animal species and tissues from which the material is a derivative; country of origin of the material, its previous use and acceptance.
4. Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the active pharmaceutical ingredient from the current and proposed manufacturers/sites.
5. The variation application form should clearly outline the previously approved and proposed manufacturers as listed in Section 2.5 of the application form.
6. A declaration by the qualified person of each of the manufacturing authorization holders listed in the application where the active pharmaceutical ingredient is used as a starting material or a declaration by the qualified person of each of the manufacturing authorization holders listed in the application as those carrying out the batch release stage. These declarations should state that the active pharmaceutical ingredient manufacturer referred to in the application carries out its activities in accordance with the Rules of Good Manufacturing Practice. A single declaration may be acceptable under certain circumstances – see the note under variation B.II.b.1.
7. Where relevant, a commitment of the active pharmaceutical ingredient manufacturer to inform the marketing authorization holder of any changes to the manufacturing process, specifications, and analytical procedures of the active pharmaceutical ingredient.
8. Proof that the proposed site is appropriately authorized for the manufacturing operation concerned.
9. Documents confirming that the active pharmaceutical ingredient manufacturer is part of the same pharmaceutical group (e.g. a letter of

confirmation).			
Note: <*>	In appropriate cases, it is also necessary to submit comparative dissolution profile data for the medicinal product with the active pharmaceutical ingredient produced at the previous site and two batches of the medicinal product with the active pharmaceutical ingredient produced at the new manufacturing site.		
B.I.a.2. Changes in the manufacturing process of the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
a) Minor change in the manufacturing process of the active pharmaceutical ingredient	1, 2, 3, 4, 5, 6, 7	1, 2, 3	IA
b) Substantial change to the manufacturing process of the active pharmaceutical ingredient which may have a significant impact on the quality, safety, or efficacy of a medicinal product	–	–	II
c) The change refers to a biological substance or use of a different chemically derived substance in the manufacture of a biological substance, which may have a significant impact on the quality, safety, and efficacy of the medicinal product and is not related to a post-approval change management protocol	–	–	II
d) The change relates to a herbal medicinal product and there is a change to any of the following: geographical source of herbal substances, manufacturing route, or production	–	–	II
e) Minor change to the Restricted Part of the APIMF	–	1, 2, 3, 4	IB

Conditions

1. No adverse change in the qualitative and quantitative impurity profile or in physico-chemical 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 pharmaceutical ingredient or intermediates are unchanged.
4. The change is fully described in the open part (Applicant's Part) of the APIMF (if applicable).
5. The active pharmaceutical ingredient is not a biological substance.
6. The change does not refer to the geographical source of herbal substances, manufacturing route, or production of a herbal medicinal product.
7. The change does not refer to the Restricted Part of the APIMF.

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application, 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. Copies of approved specifications of the active pharmaceutical ingredient (in the form of a link to the relevant document in the marketing authorization application sequence or an annex to the cover letter).
4. Proof from the marketing authorization holder or the APIMF holder, where applicable, that there is no change in the qualitative and quantitative impurity profile or in physico-chemical properties, that the synthetic route remains the same and that the specifications of the active pharmaceutical ingredient or intermediates are unchanged.

Note	Substantial changes in active pharmaceutical ingredients obtained by chemical synthesis refer to changes to the synthetic route or manufacturing conditions which may have a potential to change important quality characteristics of the active pharmaceutical ingredients, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting bioavailability.

B.I.a.3. Change in batch size (including batch size ranges) of the active pharmaceutical ingredient or intermediate used in the manufacturing process of the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
a) Up to 10-fold increase	1, 2, 3, 4,	1, 2, 5	IA

compared to the originally approved batch size	5, 6, 7, 8		
b) Up to 10-fold decrease compared to the originally approved batch size	1, 2, 3, 4, 5	1, 2, 5	IA
c) The change requires assessment of the comparability of a biological active pharmaceutical ingredient	–	–	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 active pharmaceutical ingredient is increased/decreased without process change (e.g. duplication of line)	–	1, 2, 3, 4	IB

Conditions

1. Any changes to the manufacturing methods affect only processes necessitated by batch size 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 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 pharmaceutical ingredient/intermediates remain the same.
7. The active pharmaceutical ingredient is not sterile.
8. The batch size is within the 10-fold range of the batch size provided for 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 marketing authorization application.
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 pharmaceutical ingredient 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 actions).
4. Copies of approved specifications of the active pharmaceutical ingredient (and of the intermediate, if applicable) (in the form of a link to the relevant document in the dossier sequence or an annex to the cover letter).
5. A declaration from the marketing authorization holder or the APIMF 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 pharmaceutical ingredient/intermediates remain the same.

B.I.a.4. Change to in-process tests or acceptance criteria applied during the manufacture of the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
a) Tightening of in-process acceptance criteria	1, 2, 3, 4	1, 2	IA
b) Addition of a new in-process test or acceptance criteria	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 acceptance criteria, which may have a significant effect on the overall quality of the active pharmaceutical ingredient	–	–	II
e) Deletion of an in-process test which may have a significant effect on the overall quality of the active pharmaceutical ingredient	–	–	II
f) Addition or replacement of an in-process test for safety or quality reasons	–	1, 2, 3, 4, 6	IB
g) Minor change to the analytical procedure of in-process control	8, 9, 10, 11	1, 7, 8	IA
Conditions			

1. The change is not a consequence of any commitment from previous assessments to review specification acceptance criteria (e.g. made during the procedure for marketing authorization 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 acceptance criteria.
4. The analytical procedure remains the same, or changes in the analytical procedure are minor.
5. No new test method concerns 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 pharmaceutical ingredient (except for 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 pharmaceutical ingredient), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any change in the frequency of testing.
8. Appropriate validation studies have been performed in accordance with the acts of the Union's governing bodies in the field of medicines circulation and show that the updated analytical procedure is at least equivalent to the former analytical procedure.
9. The limits of the total impurities are not changed, and no new unqualified impurities are detected.
10. The method of analysis remains the same, and changes in the analytical procedure are minor (e.g. a change in column length or temperature, but not a different type of column).
11. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active pharmaceutical ingredient (except for standard pharmacopoeial microbiological methods).

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application.
2. Comparative table of current and proposed in-process tests.
3. Details of any new non-pharmacopoeial analytical procedure and validation data, where relevant.
4. Batch analysis data on two production batches (three production batches for biologicals, unless otherwise justified) of the active pharmaceutical ingredient for all specification parameters.
5. Justification/risk assessment from the marketing authorization holder or the APIMF holder, as appropriate, that the in-process tests are non-significant, or that the in-process tests are obsolete.
6. Justification from the marketing authorization holder or APIMF holder as appropriate for the new in-process test and limits.
7. Comparative table of changes in the analytical procedure.

8. Details of any new non-pharmacopoeial analytical procedure and validation data (where relevant) confirming that the updated analytical procedure is at least equivalent to the previous one.			
B.I.a.5. Changes to the active pharmaceutical ingredient of a seasonal, prepandemic, or pandemic influenza vaccine	Conditions to be fulfilled	Documents and data	Procedure
a) Replacement of the strain(s) in a seasonal, prepandemic, or a pandemic influenza vaccine	–	–	II

B.I.b) Control of the active pharmaceutical ingredient

B.I.b.1. Change in the specification parameters and/or acceptance criteria of an active pharmaceutical ingredient, starting material/intermediate/ reagent used in the manufacturing process of the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
a) Tightening of specification acceptance criteria for biological medicinal products (containing the active pharmaceutical ingredient) subject to batch release by the official control authority of a Member State	1, 2, 3, 4	1, 2	IAIN
b) Tightening of specification acceptance criteria	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, 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	–	–	II

parameter which may have a significant effect on the overall quality of the active pharmaceutical ingredient and/or the finished product			
f) Change outside the approved range of specification acceptance criteria for the active pharmaceutical ingredient	–	–	II
g) Widening of the approved specification acceptance criteria for starting materials/intermediates, which may have a significant effect on the overall quality of the active pharmaceutical ingredient and/or the medicinal product	–	–	II
h) Addition or replacement (excluding a biological substance) of a specification parameter with its corresponding test method for safety or quality reasons	–	1, 2, 3, 4, 5, 7	IB
i) Where there is no monograph for the active pharmaceutical ingredient in the Pharmacopoeia of the Union or another pharmacopoeia according to the Concept, a change in specification from in-house to a pharmacopoeia of a third country	–	1, 2, 3, 4, 5, 7	IB
j) Addition or replacement of a specification parameter with its corresponding test method for a biological/immunological active pharmaceutical ingredient	–		II
Conditions 1. The change is not a consequence of any commitment from previous			

assessments to review specification acceptance criteria (e.g. made during the procedure for the marketing authorization of a medicinal product 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 acceptance criteria.
4. The analytical procedure remains the same, or changes in the analytical procedure are minor.
5. Any new test method is based on the general analysis methods described in the Pharmacopoeia of the Union or otherwise on methods described in other pharmacopoeias in accordance with the Concept (e.g., high-performance liquid chromatography (HPLC), spectrophotometry, titrimetry, etc.).
6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active pharmaceutical ingredient (except for standard pharmacopoeial microbiological methods).
7. For any material, the change does not concern a genotoxic impurity. If the change involves the active pharmaceutical ingredient, other than for residual solvents which must be in line with the limits specified in the relevant monograph in the Pharmacopoeia of the Union, any new impurity control should be in line with the Pharmacopoeia of the Union or otherwise any other pharmacopoeia in accordance with the Concept.
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 pharmaceutical ingredient), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water, any skip of testing.

Documentation
1. Amendment of the relevant section(s) of the marketing authorization application.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical procedure and validation data, where relevant.
4. Batch analysis data on two production batches (three production batches for biologicals, unless otherwise justified) of the relevant substance for all specification parameters.
5. Where appropriate, comparative dissolution profile data for the medicinal product containing the active pharmaceutical ingredient on at least one pilot batch complying with the current and proposed specifications. For herbal medicinal products, comparative disintegration data may be sufficient.
6. Justification/risk assessment from the marketing authorization holder or the APIMF holder, as appropriate, that the in-process parameter is non-significant, or that the in-process parameter is obsolete.
7. Justification from the marketing authorization holder or the APIMF holder, as appropriate, of the new specification parameter and the acceptance criteria.

B.I.b.2. Change in the	Conditions to be	Documents and	Procedure

analytical procedure for the active pharmaceutical ingredient or the starting material/intermediate/reagent used in the manufacturing process of the active pharmaceutical ingredient	fulfilled	data	
a) Minor changes to an approved analytical procedure	1, 2, 3, 4	1, 2	IA
b) Deletion of an analytical procedure for the active pharmaceutical ingredient or a starting material/intermediate/reagent, if an alternative analytical procedure is already authorized	7	1	IA
c) Other changes to an analytical procedure (including replacement or addition) for a reagent, which do not have a significant effect on the overall quality of the active pharmaceutical ingredient	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 an analytical procedure (including addition or replacement) for the active pharmaceutical ingredient or a starting material/intermediate	–	1, 2	IB
Conditions 1. Appropriate validation studies have been performed in accordance with the acts of the Union's governing bodies in the field of medicines circulation and show that the updated analytical procedure is at least equivalent to the former analytical procedure. 2. There have been no changes of the total impurity limits; no new unqualified impurities have been detected.			

3. The method of analysis remains 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 pharmaceutical ingredient (except for standard pharmacopoeial microbiological methods). 5. Any new test method is based on the general analysis methods described in the Pharmacopoeia of the Union or otherwise in the pharmacopoeia of a Member State or otherwise any other pharmacopoeia according to the Concept (e.g., HPLC, spectrophotometry, titrimetry, etc.). 6. The active pharmaceutical ingredient is not biological. 7. An alternative analytical procedure is already authorized for the specification parameter.
Documentation 1. Amendment to the relevant section(s) of the marketing authorization application, 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 analytical procedure.

B.I.c) Container closure system

B.I.c.1. Change in primary packaging of the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
a) Qualitative and/or quantitative composition (change in the composition of the packaging material, change in the packaging material or material quality standard)	1, 2, 3	1, 2, 3, 4, 6	IA
b) Qualitative and/or quantitative composition (change in the composition of the packaging material, change in the packaging material or material quality standard) for sterile and non-frozen biological active pharmaceutical ingredients	–	–	II
c) Qualitative and/or quantitative composition (change in the composition of	–	1, 2, 3, 5, 6	IB

the packaging material, change in the packaging material or material quality standard) for liquid active pharmaceutical ingredients (non-sterile)			

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 in accordance with the acts of the Union's governing bodies in the field of medicines circulation, and relevant stability parameters have been assessed in at least two pilot scale or industrial batches, and at least three months satisfactory stability data are at the disposal of the applicant at time of implementation. If the proposed packaging is more resistant than the existing packaging, the three months' stability data do not yet have to be available. These studies must be finalized and the data will be provided immediately to the authorized authorities if outside specifications or potentially outside specifications at the end of the shelf-life/retest period (with proposed actions).
3. Sterile, liquid and biological active pharmaceutical ingredients are excluded.

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application.
2. Appropriate data on the new packaging (e.g. comparative data on permeability, e.g. for O_2, CO_2, moisture, etc.), including a confirmation that the material complies with relevant pharmacopoeial requirements or the acts of the Union's governing bodies on the safety of materials in contact with food products or otherwise with the legislation of the Member States to the extent not regulated by the acts of the Union's governing bodies.
3. Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. there is no migration of components of the proposed material into the content or loss of components of the active pharmaceutical ingredient into the pack), including confirmation that the material complies with relevant pharmacopoeial requirements or the acts of the Union's governing bodies on the safety of materials in contact with food products or otherwise with the legislation of the Member States to the extent not regulated by the acts of the Union's governing bodies.
4. A declaration from the marketing authorization holder or the APIMF holder as appropriate that the required stability studies have been started in accordance with the acts of the Union's governing bodies in the field of medicines circulation (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 authorized authorities if outside specifications or potentially outside specifications at the end of the approved shelf life/retest period (with proposed actions).

5. The results of stability studies that have been carried out in accordance with the acts of the Union's governing bodies in the field of medicines circulation, on the relevant stability parameters, on at least two pilot or industrial batches, covering a minimum period of three months, and an assurance that these studies will be finalized, and that data will be provided immediately to the authorized authorities if outside specifications or potentially outside specifications at the end of the approved retest period (with proposed actions).
6. Comparison of current and proposed primary packaging specifications, if applicable.

B.I.c.2. Change in the specification parameters and/or acceptance criteria of the primary packaging of the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
a) Tightening of specification acceptance criteria	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 for safety or quality reasons	–	1, 2, 3, 4, 6	IB

Conditions
1. The change is not a consequence of any commitment from previous assessments to review specification acceptance criteria (e.g. made during the procedure for the marketing authorization of a medicinal product or a type II variation procedure) unless it has been previously reviewed 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 pharmaceutical ingredient.
3. Any change should be within the range of currently approved acceptance criteria.
4. The analytical procedure remains the same, or changes in the analytical procedure are minor.
5. Any new test method is based on the general analysis methods described in

the Pharmacopoeia of the Union or otherwise in the pharmacopoeia of a Member State or otherwise any other pharmacopoeia according to the Concept (e.g., HPLC, spectrophotometry, titrimetry, etc.).			
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application. 2. Comparative table of current and proposed specifications. 3. Details of any new analytical procedure and validation data, where relevant. 4. Batch analysis data on two batches of the packaging material for all specification parameters. 5. Justification/risk assessment from the marketing authorization holder or the APIMF 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 APIMF holder, as appropriate, of the new specification parameter and the acceptance criteria.			
B.I.c.3. Change in the analytical test procedure for the primary packaging of the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
a) Minor changes to an approved analytical procedure	1, 2, 3	1, 2	IA
b) Other changes to an analytical procedure (including replacement or addition)	1, 3, 4	1, 2	IA
c) Deletion of an analytical procedure if an alternative analytical procedure is already authorized	5	1	IA
Conditions 1. Appropriate validation studies have been performed according to the acts of the Union's governing bodies in the field of medicines circulation and show that the updated analytical procedure is at least equivalent to the former analytical procedure. 2. The method of analysis remains the same (e.g. a change in column length or temperature, but not a different type of column or method). 3. No new test method concerns a novel non-standard technique or a standard technique used in a novel way. 4. The active pharmaceutical ingredient/medicinal product is not biological. 5. There is still an analytical procedure registered for the specification parameter.			
Documentation			

1. Amendment to the relevant section(s) of the marketing authorization application, 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 analytical procedure.

B.I.d) Stability

B.I.d.1. Change in the retest period/storage period or storage conditions of the active pharmaceutical ingredient where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved marketing authorization application	Conditions to be fulfilled	Documents and data	Procedure
a) Retest period/storage period			
1. Reduction of the retest period	1	1, 2, 3	IA
2. Extension of the retest period based on extrapolation of stability data not in accordance with the acts of the Union's governing bodies in the field of medicines circulation<*>	–	–	II
3. Extension of storage period of a biological active pharmaceutical ingredient 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 pharmaceutical ingredient	1	1, 2, 3	IA

2. Change in storage conditions of biological active pharmaceutical ingredients, 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 pharmaceutical ingredient	–	1, 2, 3	IB
c) Change of the approved stability study program	1, 2	1, 4	IA
Conditions 1. The change should not be the result of unexpected events arising during manufacture or of a stability change. 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 marketing authorization application. 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 batches of the active pharmaceutical ingredient 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 conducted in accordance with the currently approved program. The study results must show that the agreed relevant specifications are still met. 3. Copies of approved specifications of the active pharmaceutical ingredient or link to the relevant document in the marketing authorization application. 4. Justification for the proposed changes.			
<*> Note	Retest period not applicable for biological active pharmaceutical ingredients.		

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 pharmaceutical ingredient, concerning:	Conditions to be fulfilled	Documents and data	Procedure
a) One unit operation in the manufacturing process of the	–	1, 2, 3	II

active pharmaceutical ingredient, including the resulting in-process controls and/or analytical procedures			
b) Analytical procedures for starting materials/reagents/ intermediates and/or the active pharmaceutical ingredient	–	1, 2, 3	II
Documentation 1. The design space has been developed in accordance with the acts of the Union's governing bodies in the field of medicines circulation and international scientific guidelines. Results from product, process and analytical development studies (e.g. interaction of the different parameters forming the design space to be studied, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic mechanistic understanding of material attributes, process parameters and the critical quality attributes of the active pharmaceutical ingredient 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 marketing authorization application.			
B.I.e.3. Deletion of an approved change management protocol related to the active pharmaceutical ingredient	Conditions to be fulfilled	Documents and data	Procedure
	1	1, 2	IA_{IN}
Conditions 1. The deletion of the approved change management protocol related to the active pharmaceutical ingredient 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 marketing authorization application.			
Documentation 1. Justification for the proposed deletion. 2. Amendment of the relevant section(s) of the marketing authorization application.			
B.I.e.4. Changes to an approved change management protocol	Conditions to be fulfilled	Documents and data	Procedure
a) Major changes to an	–	–	II

approved change management protocol			
b) Minor changes to an approved change management protocol that do not change the strategy defined in the protocol	–	1	IB
Documentation 1. A declaration of the manufacturer's qualified person that any change should be within the range of currently approved acceptance criteria. In addition, a declaration that an assessment of comparability is not required for biological medicinal products.			
B.I.e.5. Implementation of changes provided for in an approved change management protocol	Conditions to be fulfilled	Documents and data	Procedure
a) The implementation of the change requires no further supportive data	1	1, 3	IA_{IN}
b) The implementation of the change requires further supportive data	–	1, 2, 3	IB
c) Implementation of a change for a biological medicinal product	–	1, 2, 3, 4	IB
Conditions 1. The proposed change has been performed fully in accordance with the approved change management protocol.			
Documentation 1. A declaration that the change is in accordance with the approved change management protocol and that the study results meet the acceptance criteria specified in the protocol. In addition, a declaration that an assessment of comparability is not required for biological medicinal products. 2. Results of the studies performed in accordance with the approved change management protocol. 3. Amendment of the relevant section(s) of the marketing authorization application. 4. Copies of approved specifications of the active pharmaceutical ingredient or link to the relevant section in the marketing authorization application.			

B.II. 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	Documents and data	Procedure
a) Changes in imprints, bossing or other markings	1, 2, 3, 4	1	IA
b) Changes in scoring/break lines intended to divide into equal doses	–	1, 2, 3	IB
Conditions 1. Medicinal 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 marketing authorization application, including a detailed drawing or written description of the current and new appearance and revised product information as appropriate. 2. Subject to agreement with the expert organization, samples of the medicinal product and/or their visual image to assess the appearance. 3. Results of the appropriate tests demonstrating equivalence in characteristics/dosing accuracy and conducted under the Pharmacopoeia of the Union or otherwise the Pharmacopoeia of a Member State or otherwise any other pharmacopoeia according to the Concept.			
B.II.a.2 Change in the shape or dimensions of the dosage form	Conditions to be fulfilled	Documents and data	Procedure
a) Immediate release tablets, capsules, suppositories and pessaries	1, 2, 3, 4	1, 4	IA
b) Gastro-resistant, modified or prolonged release dosage 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 medicinal product with the new dosage form or dosage form dimensions is comparable to the dissolution profile of the medicinal product with the old dosage form or dosage form dimensions. For herbal medicinal products, where equivalence dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one. 2. Medicinal product release and end-of-shelf life specifications have not been changed (except for dosage form 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 marketing authorization application, including a detailed drawing of the authorized and proposed dosage form and 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 in accordance with the Rules for Conducting Bioequivalence Studies). For herbal medicinal products, comparative disintegration data may be acceptable. 3. Justification for not submitting a new bioequivalence study according to the Rules for Conducting Bioequivalence Studies. 4. Samples of the medicinal product and/or its visual image, where applicable, subject to agreement with the expert organization. 5. Results of the appropriate tests demonstrating equivalence in characteristics/dosing accuracy and conducted under the Pharmacopoeia of the Union or otherwise the Pharmacopoeia of a Member State or otherwise any other pharmacopoeia according to the Concept.			
<*> Note	For B.II.a.2.c), any change to the strength of the medicinal product requires the submission of an extension application, with the exception of aligning the marketing authorization application with the Union requirements if the new strength is authorized in accordance with the legislation of a Member State in only one of the Member States stated as part of the alignment procedure.		
B.II.a.3. Changes in the composition (excipients) of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Changes in components of the flavoring or coloring system			
1. Addition, deletion or replacement	1, 2, 3, 4, 5, 6, 7, 9, 10	1, 2, 4, 5, 6	IA

2. Increase or reduction	1, 2, 3, 4, 10	1, 2, 4	IA
b) Other excipients			
1. Any minor adjustment of the quantitative composition of the medicinal 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 medicinal 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 and/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 dosage 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 dosage form.
3. The medicinal 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 (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot or industrial batches and at least three 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 the marketing authorization holder will report to the

authorized authority the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions). In addition, where relevant, photostability testing should be performed.

5. Any new proposed components must comply with the requirements of the Union's regulatory acts for colors for use in foodstuffs and flavors.
6. No new component involves the use of materials of human or animal origin for which assessment is required of viral safety data or compliance with the current requirements of the Pharmacopoeia of the Union (and/or other pharmacopoeias according to the Concept) on minimizing the risk of transmitting animal spongiform encephalopathy agents via human medicinal products.
7. Where applicable, the change does not affect the possibility of differentiation between strengths and does not have a negative impact on taste acceptability for pediatric formulations.
8. The dissolution profile of the new medicinal product determined on a minimum of two pilot scale batches is comparable to the old one (no significant differences regarding dissolution profile comparability in accordance with the Rules for 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. possibility of differentiation between strengths.
10. The product concerned is not a biological medicinal product.

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application, including the identification test method for any new colorant, where relevant, and revised product information as appropriate.
2. Proof from the marketing authorization holder that the required stability studies have been started (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 the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).
3. The results of stability studies on the relevant stability parameters on at least two pilot or industrial batches, covering a minimum period of three months, and an assurance that these studies will be finalized and that the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).
4. Samples of the medicinal product and/or its visual image, where applicable, subject to agreement with the expert organization.
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

authorized authority and shown to comply with the scope of the current monograph of the Pharmacopoeia of the Union (or other pharmacopoeias according to the Concept) on minimizing the risk of transmitting animal spongiform encephalopathy agents via human 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 analytical procedures of the medicinal product specification, 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 medicinal product in the new and old composition. For herbal medicinal products, comparative disintegration data may be sufficient.
9. Justification for not submitting a new bioequivalence study in accordance with the Rules for Conducting Bioequivalence Studies.

B.II.a.4. Change in the coating weight of oral dosage forms or change in the weight of capsule shells	Conditions to be fulfilled	Documents and data	Procedure
a) Solid oral dosage forms	1, 2, 3, 4	1, 2	IA
b) Gastro-resistant, modified or prolonged release dosage forms where the coating is a critical factor for the release mechanism	–	–	II

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 medicinal product specification has only been updated in respect of weight and dimensions, if applicable.
4. Stability studies have been started with at least two pilot scale or industrial scale batches, and at least three months satisfactory stability data are at the disposal of the applicant at the time of implementation, and an assurance is given that these studies will be finalized. The marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application.
2. A declaration from the marketing authorization holder that the required stability studies have been started (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the marketing authorization holder 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 the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions). In addition, where relevant, photostability testing should be performed.

B.II.a.6. Deletion of the solvent/diluent container from the pack	Conditions to be fulfilled	Documents and data	Procedure
	–	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 medicinal product information.

B.II.a.7. Changes that are an extension of marketing authorization for the medicinal product strength<*>	Conditions to be fulfilled	Documents and data	Procedure
	1, 2, 3	1, 2, 3	IB

Conditions
1. The strengths added or introduced to replace the previously authorized ones must be authorized in at least one of the Member States at the time of submitting an application for the marketing authorization application alignment.
2. At the time of submitting the application for the marketing authorization application alignment, the lowest and highest strengths, or the strength determined on the basis of the risk analysis, for which appropriate bioequivalence studies or clinical trials have been conducted, the results of which can be extrapolated to the remaining strengths, must be authorized in the reference Member State.
3. The biowaiver criteria for additional strengths described in the Rules for Conducting Bioequivalence Studies must be met.

Documentation
1. Copies of marketing authorization certificates confirming the marketing authorization of newly declared dosages.

2. Module 3 of the marketing authorization application for each new strength in accordance with Part I of Appendix 1 hereto. The existing sections may be modified to add information about strengths, as appropriate. 3. Rationale for the possibility of extrapolating the results of bioequivalence studies for new strengths applied for the biowaiver. In the case of a biowaiver based on the biopharmaceutical classification system, the conditions of the biowaiver shall be met for each strength.	
<*> Note	Any change to the strength of the medicinal product requires the submission of an extension application.

B.II.b) Manufacture

B.II.b.1. Replacement or addition of a manufacturing site for a part or all of the manufacturing process of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
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, 10	IA
c) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological medicinal products or for dosage forms manufactured by complex production 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, 10	IB
f) Site where any manufacturing operation(s) take place, except batch release, batch control and secondary packaging, for sterile medicinal products	–	1, 2, 3, 4, 5, 7, 8, 10	IB

(including those that are aseptically manufactured) excluding biological medicinal products			

Conditions

1. Satisfactory inspection in the last three years by the inspection authorities of the Member States or of a country with which an operational agreement exists on mutual recognition of Good Manufacturing Practice certificates.
2. Site appropriately authorized (to manufacture the dosage form or product concerned).
3. The product concerned is not a sterile product.
4. Where relevant, for instance, for suspensions and emulsions, the process validation plan is available or validation of the manufacture at the new site has been successfully carried out in accordance with the current protocol with at least three production batches.
5. The product concerned is not a biological medicinal product.

Documentation

1. Proof that the proposed site is appropriately authorized for the dosage form or product concerned.
2. Where relevant, the batch numbers, corresponding batch size and the manufacturing date of batches (≥ 3) used in the validation study should be indicated and the validation data presented or validation protocol submitted.
3. The paragraph of the variation application form on changes (cover letter or variation application form attached to the cover letter) should clearly outline the previously approved and proposed manufacturers as listed in Section 2.5 of the application form.
4. Copies 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 (including the equivalence dissolution test in appropriate cases) on the last three batches from the previous site. Batch data on the next two full production batches should be made available upon request and reported if outside specification (with proposed actions).
6. For semi-solid and liquid dosage forms in which the active pharmaceutical ingredient 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 pharmaceutical ingredient as a starting material – a declaration by the qualified person at the site responsible for batch release that the active pharmaceutical ingredient is manufactured in accordance with the Rules of Good Manufacturing Practice for starting materials.
8. Amendment of the relevant section(s) of the marketing authorization application.
9. If the manufacturing site and the primary packaging site are different, conditions of transportation and bulk storage should be specified and

validated. 10. Valid document certifying the compliance of the finished dosage form manufacturing site(s) with the requirements of the Union's Good Manufacturing Practice.	
Notes:	Declarations of an qualified person concerning an active pharmaceutical ingredient Manufacturing authorization holders are obliged to only use as starting materials active pharmaceutical ingredients that have been manufactured in accordance with the Rules of Good Manufacturing Practice, so a declaration is expected from each of the manufacturing authorization holders that use the active pharmaceutical ingredient as a starting material. In addition, as the qualified person responsible for batch certification takes overall responsibility for each batch, a further declaration from the qualified person responsible for batch certification is expected when the batch release site is a different site from the dosage form manufacturer. In many cases only one manufacturing authorization holder is involved and therefore only one declaration shall 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 qualified person. This will be accepted provided that: The declaration makes it clear that it is signed on behalf of all the involved qualified persons. The arrangements are underpinned by a technical agreement as described in Chapter 7 of the Rules of Good Manufacturing Practice, and the qualified person providing the declaration is the one identified in the agreement as taking specific responsibility for the compliance of the active pharmaceutical ingredient manufacturer(s) with the Rules of Good Manufacturing Practice. Note: these arrangements are subject to inspection by the authorized authorities.

B.II.b.2. Change of the manufacturer responsible for the quality control of the medicinal product and the batch release of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Replacement or addition of a site where batch control/testing takes place	1, 2, 3	3, 4	IA
b) Replacement or addition of a site where batch control/testing takes place for a			II

biological medicinal product and any of the test methods performed at the site is a biological/immunological/immunochemical method			
c) Replacement or addition of a manufacturer responsible for batch release			
1. Not including batch control/testing	1	1,2,3	IA_{IN}
2. Including batch control/testing	1, 2	1,2,3	IA_{IN}
3. Including batch control/testing for a biological medicinal product and any of the test methods performed at that site is a biological/ immunological/immunochemical method			II
Conditions 1. The site is appropriately authorized. 2. The product is not a biological medicinal product. 3. The transfer of analytical procedures from the old to the new testing laboratory has been successfully completed.			
Documentation 1. The cover letter or variation application form attached to the cover letter should clearly outline the previously approved and proposed manufacturers. 2. A declaration by the qualified person responsible for batch release stating that active pharmaceutical ingredient manufacturers referred to in the marketing authorization application operate in accordance with the Rules of Good Manufacturing Practice for starting materials. A single declaration may be acceptable under certain circumstances (see the note under variation B.II.b.1). 3. Amendment of the relevant section(s) of the marketing authorization application, including product information and, as appropriate, data on the validation (verification) of analytical procedures transferred from the old site to the new one, in accordance with the acts of the Union's governing bodies in the field of transfer of technologies and analytical procedures. 4. Valid document certifying the compliance of the finished dosage form manufacturing site(s) carrying out batch release with the Rules of Good Manufacturing Practice.			
B.II.b.3. Change in the	Conditions to be	Documents	Procedure

manufacturing process of the medicinal product, including an intermediate used in the manufacture of the medicinal product	fulfilled	and data	
a) Minor change in the manufacturing process	1, 2, 3, 4, 5, 6, 7	1, 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 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 pharmaceutical ingredient	–	–	II
f) Minor change in the manufacturing process of an aqueous oral suspension and other specialized dosage forms	–	1, 2, 4, 6, 7, 8	IB
g) Change in the medicinal product manufacturing process: relocation of sterile filtration from the Grade A/B area to the Grade C area	–	–	II
h) Change in the secondary packaging material of a bulk product that does not come into direct contact with this product (including replacement and addition)	8	1	IA
Conditions 1. No change in the qualitative and quantitative impurity profile or in physico-			

chemical properties.

2. The change relates to:
   an immediate release solid oral or topical dosage form;
   liquid dosage forms in the form of solutions, semi-solid dosage forms and suppositories that do not belong to specialized dosage forms manufactured by non-standard processes in accordance with the acts of the Union's governing bodies in the field of medicines circulation. Moreover, the change relates to process parameter(s) that have been considered to have no impact on the quality of the medicinal product (regardless of the type of medicinal product and/or dosage form) and the medicinal product concerned is not a biological or herbal medicinal product.
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 acceptance criteria) are required to these controls.
5. The specifications of the medicinal 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 Union's relevant documents have been started with at least one pilot or industrial batch, and at least three months stability data are at the disposal of the applicant. Assurance is given that the studies will be finalized and that the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).
8. The secondary packaging is not functional to ensure the stability or is at least equivalent in relevant properties to the approved one.

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application.
2. For semi-solid and liquid dosage forms in which the active pharmaceutical ingredient 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. Batch data on the next two full production batches should be made available upon request or reported if outside specification (with proposed actions). For herbal medicinal products, comparative disintegration data may be sufficient.
4. Justification for not submitting a new bioequivalence study in accordance with the Union Rules for Conducting Bioequivalence Studies.
5. For changes to process parameter(s) that have been considered to have no impact on the quality of the medicinal product, a declaration to this effect reached in the context of the previously approved risk assessment.

6. Copies of release and end-of-shelf life specifications (in the form of a link to the relevant document in the dossier sequence or an annex to the cover letter). 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 if outside specification (with proposed actions). 8. Proof from the marketing authorization holder that relevant stability studies have been started (with indication of the batch numbers concerned) and relevant stability parameters have been assessed in at least one pilot or industrial batch and at least three 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 the studies will be finalized and that the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).

B.II.b.4. Change in the batch size (including batch size ranges) of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Up to 10-fold increase compared to the originally approved batch size	1, 2, 3, 4, 5, 7	1, 4	IA
b) Up to 10-fold decrease compared to the originally approved batch size	1, 2, 3, 4, 5, 6	1, 4	IA
c) The change requires assessment of the comparability of a biological medicinal product or the change in batch size requires a new bioequivalence study	–	–	II
d) The change relates to all other dosage forms manufactured by complex manufacturing processes	–	–	II
e) More than 10-fold increase compared to the originally approved batch size for immediate release (oral) dosage forms	–	1, 2, 3, 4, 5, 6	IB
f) The scale for a biological medicinal product is	–	1, 2, 3, 4, 5, 6	IB

increased/decreased without process change (e.g. duplication of line)			

Conditions

1. The change does not affect reproducibility and/or consistency of the product.
2. The change relates to conventional immediate release oral dosage forms or to non-sterile liquid dosage 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 industrial batches at the proposed new batch size in accordance with the relevant guidelines.
5. The product concerned is not a biological medicinal product.
6. The change should not be the result of unexpected events arising during manufacture or of a stability change.
7. The batch size is within the 10-fold range of the batch size provided for 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 marketing authorization application.
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 (including the equivalence dissolution test in appropriate cases). Batch data on the next two full production batches should be made available upon request and reported by the MAH if outside specification (with proposed actions).
3. Copies of approved release and end-of-shelf life specifications (in the form of a link to the relevant document in the dossier sequence or an annex to the cover letter).
4. Where relevant, the numbers of batches, a new 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 on the relevant stability parameters on at least one pilot or industrial batch, covering a minimum period of three months, and an assurance that these studies will be finalized and that the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions). For biological medicines: a declaration that an assessment of comparability is not required.

B.II.b.5. Change to in-process tests or acceptance criteria	Conditions to be fulfilled	Documents and data	Procedure

applied during the manufacture of the medicinal product			
a) Tightening of in-process acceptance criteria	1, 2, 3, 4	1, 2	IA
b) Addition of a new test(s) and acceptance criteria	1, 2, 5, 6	1, 2, 3, 4, 5, 7, 8	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 medicinal product	–	–	II
e) Widening of the approved in-process control acceptance criteria, which may have a significant effect on the overall quality of the medicinal product	–	–	II
f) Addition or replacement of an in-process test for safety or quality reasons	–	1, 2, 3, 4, 5, 7, 8	IB
g) Minor change to the analytical procedure of in-process control	4, 6, 8, 9	1, 2, 3	IA

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification acceptance criteria (e.g. made during the procedure for marketing authorization 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 acceptance criteria.
4. The method of analysis remains the same, and the analytical procedure remains the same, or changes in the analytical procedure are minor (e.g. a change in column length or temperature, but not a different type of column).
5. No new test method concerns 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 pharmaceutical ingredient (except for 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 or tapped density, etc.); identity test (unless there is a suitable alternative control already present); microbiological control (unless not required for the particular dosage form). 8. Appropriate validation studies have been performed in accordance with the acts of the Union's governing bodies in the field of medicines circulation and show that the updated analytical procedure is at least equivalent to the former analytical procedure. 9. The limits of the total impurities are not changed, and no new unqualified impurities are detected.
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application. 2. Comparative table of current and proposed in-process tests and acceptance criteria or comparative table of changes in the analytical procedure. 3. Details of any new analytical procedure and validation data (where relevant) confirming that the updated analytical procedure is at least equivalent to the previous one. 4. Batch analysis data on two production batches (three production batches for biologicals, unless otherwise justified) of the medicinal product for all specification parameters. 5. Where appropriate, comparative dissolution profile data for the medicinal product on at least one pilot batch manufactured using the current and new in-process tests. 6. For herbal medicinal products, comparative disintegration data may be sufficient. 7. Justification/risk assessment showing that the in-process test is non-significant or that it is obsolete. 8. Justification of the new in-process test and acceptance criteria.

B.II.c) Control of excipients

B.II.c.1. Change in the specification parameters and/or acceptance criteria of an excipient	Conditions to be fulfilled	Documents and data	Procedure
a) Tightening of specification acceptance criteria	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	1, 2, 7	IA
d) Change outside the approved range of specification acceptance criteria	–	–	II
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the medicinal product	–	–	II
f) Addition or replacement (excluding a biological medicinal product) of a specification parameter with its corresponding test method for safety or quality reasons	–	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 pharmacopoeia according to the Concept or otherwise a pharmacopoeia not covered by the Concept	–	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 acceptance criteria (e.g. made during the procedure for the marketing authorization of the medicinal product 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 acceptance criteria.
4. The analytical procedure remains the same, or changes in the analytical procedure are minor.
5. No new test method concerns 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 pharmaceutical ingredient (except for 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);
   any critical physical characteristics (particle size, bulk or 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 marketing authorization application.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical procedure and validation data, where relevant.
4. Batch analysis data on two production batches (three production batches for biologicals, unless otherwise justified) of the excipient for all specification parameters.
5. Where appropriate, comparative dissolution profile data for the medicinal 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 sufficient.
6. Justification for not submitting a new bioequivalence study in accordance with the Rules for Conducting Bioequivalence Studies.
7. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.
8. Justification of the new specification parameter and acceptance criteria.

B.II.c.2. Change in the analytical procedure for an excipient	Conditions to be fulfilled	Documents and data	Procedure
a) Minor changes to an approved analytical procedure	1, 2, 3, 4	1, 2	IA
b) Deletion of an analytical procedure if an alternative analytical 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 an analytical procedure (including replacement or addition)	–	1, 2	IB
Conditions 1. Appropriate validation studies have been performed in accordance with the relevant documents and show that the updated analytical procedure is at least equivalent to the former analytical procedure. 2. There have been no changes of the total impurity limits; no new unqualified impurities have been detected. 3. The method of analysis remains the same (e.g. a change in column length or temperature, but not a different type of column or method). 4. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent (except for standard pharmacopoeial microbiological methods). 5. An alternative analytical procedure is already authorized for the specification parameter.			
Documentation 1. Amendment to the relevant section(s) of the marketing authorization application, 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 analytical procedure.			
B.II.c.3. Change in the source of an excipient or reagent with TSE risk	Conditions to be fulfilled	Documents and data	Procedure
a) From TSE risk material to vegetable or synthetic origin			
1. For excipients or reagents not used in the manufacture of a biological active pharmaceutical ingredient or in a biological medicinal product	1	1	IA
2. For excipients or reagents used in the manufacture of a biological active pharmaceutical ingredient or in a biological medicinal product	–	1, 2	IB
b)Change or introduction of a	–	–	II

TSE risk material or replacement of a TSE risk material from a different TSE risk material not covered by a TSE Certificate of Suitability			
c) Change in the source of an excipient with a low risk of TSE contamination	2	1, 2	IA
Conditions 1. Excipient and medicinal product release and end-of-shelf life specifications remain the same. 2. It is necessary to ensure compliance with the conditions for minimizing the risk of TSE contamination, as specified in the acts of the Union's governing bodies in the field of medicines circulation.			
Documentation 1. Proof 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 medicinal product.			
B.II.c.4. Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the marketing authorization application) or a novel excipient	Conditions to be fulfilled	Documents and data	Procedure
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 physico-chemical properties of the excipient which may affect the quality of the medicinal product	-	-	II
c) The excipient is a biological substance	-	-	II
d) Deletion of one manufacturing process of a non-pharmacopoeial excipient	3, 4	1, 4, 5	IA

(when described in the marketing authorization application for the medicinal product) or a novel excipient			
Conditions 1. The synthetic route and specifications are identical and there is no change in the qualitative and quantitative impurity profile (excluding residual solvents, provided they are controlled in accordance with the limits specified in the acts of the Union's governing bodies in the field of medicines circulation) or in physico-chemical properties. 2. The excipient is not an adjuvant. 3. At least one previously approved production process must remain unchanged. 4. The deletion should not be due to critical deficiencies concerning manufacturing.			
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application. 2. Batch analysis data (in comparative tabular 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 medicinal product on at least two batches (minimum pilot scale). For herbal medicinal products, comparative disintegration data may be sufficient. 4. Copies of approved and new (if applicable) specifications of the excipient. 5. Proof from the applicant that the deletion is not due to critical deficiencies concerning manufacturing.			

B.II.d) Control of the medicinal product

B.II.d.1. Change in the specification parameters and/or acceptance criteria of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Tightening of specification acceptance criteria	1, 2, 3, 4	1, 2	IA
b) Tightening of acceptance criteria for immunological medicinal products or human plasma-derived medicinal products subject to batch release by the official control authority of a Member State	1, 2, 3, 4	1, 2	IAIN
c) Addition of a new specification parameter to the			II

specification with its corresponding test method and/or procedure			
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	1, 2, 7	1, 2, 4	IA
e) Change outside the approved range of specification acceptance criteria	–	–	II
f) Deletion of a specification parameter which may have a significant effect on the overall quality of the medicinal product	–	–	II
g) Addition or replacement of a specification parameter with its corresponding test method for safety or quality reasons	–	–	II
h) Update of the dossier, including the normative document, to comply with the provisions of an updated general monograph of the Pharmacopoeia of the Union or (for the marketing authorization of the medicinal product in one Member State) the pharmacopoeia of a Member State (including the update of references) for the medicinal product <*>	1, 2, 3, 4, 5, 6	1, 2	IAIN
i) the test according to Monograph 2.1.9.14 of the Pharmacopoeia of the Union "Uniformity of Dosage Units" is introduced to replace the previously approved method or test according to Monograph 2.1.9.5 "Uniformity of Mass of Single-Dose Preparations"	1, 2, 8	1, 2, 3	IA

j) Reduction in the frequency of routine testing up to the deletion of testing or periodic testing (e.g. microbiological testing of the medicinal product)		1, 2, 5	IB
k) Change in the specification parameters and/or limits of the medicinal product to more accurately describe the appearance of the medicinal product	2	1, 2	IA

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification acceptance criteria (e.g. made during the procedure for the marketing authorization of the medicinal product or a type II variation procedure).
2. The change does not result from unexpected events arising during the manufacture (e.g. new unqualified impurity; change in total impurity limits) or testing of the medicinal product.
3. Any change should be within the range of currently approved acceptance criteria.
4. The procedure remains the same, or changes in the procedure are minor.
5. The change does not concern any impurities (including genotoxic) or dissolution.
6. The change concerns the updating of the acceptance criteria for microbial control to be in line with the current Pharmacopoeia of the Union or otherwise the pharmacopoeia of a Member State or otherwise any other pharmacopoeia according to the Concept, and the currently registered acceptance criteria for microbial control do not include any additional specified controls over the Pharmacopoeia requirements for the particular dosage form.
7. The specification parameter does not concern a critical parameter, e.g.:
   assay;
   impurities (unless a particular solvent is definitely not used in the manufacture of the medicinal product);
   any critical physical characteristics (hardness or friability for uncoated tablets, dimensions, etc.);
   any request for skip testing.
8. The proposed control is fully in line with the Table 2.1.9.14.-1 of the monograph of the Pharmacopoeia of the Eurasian Economic Union "Uniformity of Dosage Units" and does not include the alternative proposal for testing uniformity by mass variation instead of content uniformity when the latter is specified in the above table.

Documentation 1. Amendment of the relevant section(s) of the marketing authorization application. 2. Comparative table of current and proposed specifications. 3. Batch analysis data on two production batches (three production batches for biologicals, unless otherwise justified) of the medicinal product for all specification parameters. 4. Justification/risk assessment showing that the parameter is non-significant. 5. Justification/risk assessment showing that the frequency of testing for a parameter may be changed.	
<*> Note	There is no need to notify the authorized authorities of an updated monograph of the Pharmacopoeia of the Union or the pharmacopoeia of a Member State (for the marketing authorization of the medicinal product in one Member State) in the case that reference is made to the "current edition (in accordance with the legislation of a Member State)" in the marketing authorization application and/or the normative document of an authorized medicinal product. This variation therefore applies to cases where no reference to the updated monograph of the pharmacopoeia was contained in the marketing authorization application and/or the normative document and the variation is made to make reference to the updated version.

B.II.d.2. Change in the analytical procedure for the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Minor changes to an approved analytical procedure	1,2,3	1	IB
b) Deletion of an analytical procedure if an alternative analytical procedure is already authorized	3	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 an analytical procedure (including	–	–	II

replacement or addition)			
e) Update of the analytical procedure to comply with the updated general monograph in the Pharmacopoeia of the Union or the pharmacopoeia of a Member State (for the marketing authorization of the medicinal product in one Member State)	1,2,3,4	1	IA
f) To reflect compliance with the Pharmacopoeia of the Union or the pharmacopoeia of a Member State (for the marketing authorization of the medicinal product in one Member State) and remove reference to the outdated internal analytical procedure and its number <*>	1,2,3,4	1	IA

Conditions

1. There have been no changes of the total impurity limits; no new unqualified impurities have been detected.
2. There are no significant changes affecting the reproducibility of the analytical procedure.
3. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (except for standard pharmacopoeial microbiological methods).
4. The registered analytical procedure already refers to the general monograph of the Pharmacopoeia of the Union or the pharmacopoeia of a Member State (for the marketing authorization of the medicinal product in one Member State), and any changes are minor in nature and require the technical update of the marketing authorization application.

Documentation

1. Amendment to the relevant section(s) of the marketing authorization application, including a description of the analytical procedure, revised specifications for impurities (if applicable).

<*> Note	There is no need to notify the authorized authorities of an updated monograph of the Pharmacopoeia of the Union or the pharmacopoeia of a Member State in the case that reference is made to the “current edition (in accordance with the legislation of a Member State)” in the dossier of an authorized medicinal product.

B.II.e) Packaging (closure) system

B.II.e.1. Change in primary packaging of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Qualitative and/or quantitative composition of the material of the packaging (closure) system (primary packaging)			
1. Solid dosage forms	1, 2, 3	1, 2, 3, 4, 6	IA
2. Semi-solid and non-sterile liquid dosage forms	–	1, 2, 3, 5, 6	IB
3. Sterile medicinal products and biological 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 the primary packaging type or addition of a new primary packaging type			
1. Solid, semi-solid and non-sterile liquid dosage forms	–	1, 2, 3, 5, 6, 7	IB
2. Sterile medicinal products and biological medicinal products	–	–	II
3. Deletion of a primary packaging type that does not lead to the complete deletion of a strength or dosage form	4	1, 8	IA

Conditions

1. The change only concerns the same packaging 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, and relevant stability parameters have been assessed in at least two pilot scale or industrial batches, and at least three 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 three months' stability data do not yet have to be available. These studies must be finalized, and the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).
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 marketing authorization application.
2. Appropriate data on the new packaging (e.g. comparative data on permeability, e.g. for O_2, CO_2, moisture, etc.).
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 the acts of the Union's governing bodies on the safety of materials in contact with food products.
4. A declaration from the marketing authorization holder that the required stability studies have been started (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 the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).
5. The results of stability studies on the relevant stability parameters on at least two pilot or industrial batches, covering a minimum period of three months, and an assurance that these studies will be finalized and that the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).
6. Comparison of current and proposed primary packaging specifications, if applicable.
7. Photo and/or sketch of the new packaging (closure) system where applicable.
8. A declaration from the marketing authorization holder 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), any change which results in a "new dosage form" requires the submission of an extension application.		
B.II.e.2. Change in the specification parameters and/or acceptance criteria of the primary packaging of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Tightening of specification acceptance criteria	1, 2, 3, 4	1, 2	IA
b) Addition of a new specification parameter to the specification with its corresponding analytical procedure	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 for safety or quality reasons	–	1, 2, 3, 4, 6	IB
e) Widening of the acceptance criteria for the Total Thickness parameter of the blister foil (covering aluminum foil) in the primary packaging of solid dosage forms caused by the difference in the amount of primer material applied	6, 7	1, 2, 4, 5, 6, 7	IA

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification acceptance criteria (e.g. made during the procedure for the marketing authorization of the medicinal product 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 acceptance criteria.
4. The analytical procedure remains the same, or changes in the analytical procedure are minor.

5. Any new test procedure is based on the general analysis methods described in the Pharmacopoeia of the Union or the pharmacopoeia of a Member State (for the marketing authorization of the medicinal product in one Member State) (e.g., HPLC, spectrophotometry, titrimetry, etc.).
6. The primer material remains the same.
7. Relevant stability studies in accordance with the acts of the Union's governing bodies in the field of medicines circulation have been started with at least two pilot or industrial batches. These studies must be finalized, and data will be provided immediately to the authorized authorities if outside specifications or potentially outside specifications at the end of the approved shelf life.

Documentation
1. Amendment of the relevant section(s) of the marketing authorization application.
2. Comparative table of current and proposed specifications.
3. Details of any new analytical procedure and validation data, where relevant.
4. Batch analysis data on two batches of the packaging material for all specification parameters.
5. Justification/risk assessment showing that the parameter is non-significant.
6. Justification of the new specification parameter and acceptance criteria.
7. Proof that relevant stability studies in accordance with the acts of the Union's governing bodies in the field of medicines circulation have been started with at least two pilot or industrial batches.

B.II.e.3. Change in the analytical procedure for the primary packaging of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Minor changes to an approved analytical procedure	1, 2, 3	1, 2	IA
b) Other changes to an analytical procedure (including replacement or addition)	1, 3, 4	1, 2	IA
c) Deletion of an analytical procedure if an alternative analytical procedure is already authorized	5	1	IA

Conditions 1. Appropriate validation studies have been performed according to the relevant acts of the Union's governing bodies in the field of medicines circulation and show that the updated analytical procedure is at least equivalent to the former analytical procedure. 2. The method of analysis remains the same (e.g. a change in column length or temperature, but not a different column or method). 3. No new test method concerns a novel non-standard technique or a standard technique used in a novel way. 4. The active pharmaceutical ingredient/medicinal product is not biological. 5. An alternative analytical procedure is already authorized for the specification parameter.
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application. 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 analytical procedure.

B.II.e.4. Change in the shape or dimensions of the packaging (closure) system (primary packaging)	Conditions to be fulfilled	Documents and data	Procedure
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 medicinal product	–	–	II
c) Sterile medicinal products	–	1, 2, 3, 4	IB

Conditions

1. No change in the qualitative or quantitative composition of the primary packaging material.
2. The change does not concern a fundamental part of the packaging material which may have an impact on the delivery, use, safety or stability of the medicinal product.
3. In case of a change in the headspace or a change in the surface/volume ratio, stability studies have been started and relevant stability parameters have been assessed in at least two pilot (three for biological medicinal products) or industrial batches and at least three months (six months for biological medicinal products) stability data are at the disposal of the applicant. Assurance is given that the studies will be finalized and that the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).

Documentation

1. Amendment of the relevant section(s) of the marketing authorization application, including the description, detailed drawing and composition of the primary packaging or closure material and revised product information as appropriate.
2. Photo and/or sketch of the new packaging (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 from the marketing authorization holder that the required stability studies have been started (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 the time of implementation for a Type IA notification and the 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 the marketing authorization holder will report to the authorized authorities the data if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed actions).

B.II.e.5. Change in the pack size of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Change in the number of dosage form units (e.g. tablets, ampoules, etc.) in a pack			
1. Change within the range of the currently approved pack sizes	1, 2	1, 3	IAIN
2. Change outside the range of		1, 2, 3	IB

the currently approved pack sizes			
b) Deletion of the pack size(s)	3	1, 2	IAIN
c) Change in the fill weight/fill volume of sterile multi-dose (or single-dose, partial use) parenteral medicinal products, including biological medicinal products	–	–	II
d) Change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) medicinal products	–	1, 2, 3	IB

Conditions
1. A 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 marketing authorization application, including revised product information as appropriate.
2. Justification showing that the new/remaining pack sizes are consistent with the dosage regimen and duration of treatment as approved in the summary of product characteristics.
3. A declaration that stability studies will be conducted in accordance with the acts of the Union's governing bodies in the field of medicines circulation where stability parameters could be affected. Data to be reported only if outside specifications (with proposed actions).

Note:	For B.II.e.5.c) and B.II.e.5.d), 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 packaging (material) not in contact with the medicinal product (such as the color of flip-off caps, color code rings on ampoules, the change of needle shield (different plastic used), the change of the design (color) of intermediate or secondary	Conditions to be fulfilled	Documents and data	Procedure

packaging mock-ups, barcode application (2D, 3D) or Braille font application))			
a) Change that affects the product information specified in paragraph 1.6.1 of Appendix 19 to the Rules of Marketing Authorization	1	1	IA_{IN}
b) Change that does not affect the product information specified in paragraph 1.6.1 of Appendix 19 to the Rules of Marketing Authorization	1	1	IA
Conditions 1. The change does not concern a part of the packaging material which may have an impact on the delivery, use, safety or stability of the medicinal product.			
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application, including revised product information as appropriate.			
B.II.e.7. Change in a manufacturer of components of the packaging (closure) system (primary packaging) or additional products (including devices and component parts) (when mentioned in the marketing authorization application)	Conditions to be fulfilled	Documents and data	Procedure
a) Deletion of a manufacturer	1	1	IA
b) Replacement or addition of a manufacturer	1, 2, 3, 4	1, 2, 3	IA
c) Any change to manufacturers of spacer devices for metered dose inhalers	–	–	II
d) Change in the name of a manufacturer of a component of the packaging (closure) system (primary packaging) <*>	5	1	IA

Conditions 1. No deletion of any packaging component or device. 2. The qualitative and/or quantitative composition of materials of components of the packaging (closure) system (primary packaging) or additional products (including devices and component parts), as well as design specifications remain the same. 3. The specifications and quality control methods are at least equivalent. 4. The sterilization method and conditions remain the same, if applicable. 5. There is no change in a manufacturer of a component of the packaging (closure) system (primary packaging) or additional products (including devices and component parts).
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application. 2. Documents and information on the medical product that are attached to the medicinal product in accordance with paragraph 187 of these Rules. 3. Comparative table of current and proposed specifications, if applicable.

<*> Note	If necessary, this information is subject to deletion from the marketing authorization application for the medicinal product.

B.II.f) Stability

B.II.f.1. Change in the shelf life or storage conditions of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Reduction of the shelf life of the medicinal product			
1. As packaged in secondary packaging	1	1, 2, 3	IA_{IN}
2. After the 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 medicinal product			
1. As packaged in secondary packaging (supported by real-time data)	-	1, 2, 3	IB
2. After the first opening (supported by real-time data)	-	1, 2, 3	IB
3. After dilution or	-	1, 2, 3	IB

reconstitution (supported by real-time data)			
4. Extension of the shelf life based on extrapolation of stability data not in accordance with the acts of the Union's governing bodies in the field of medicines circulation <*>	-	-	II
5. Extension of the shelf life of a biological 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 medicinal 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 of a stability change.
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 marketing authorization application. This must contain results of appropriate real-time stability studies (covering the entire shelf life) conducted in accordance with the acts of the Union's governing bodies in the field of medicines circulation on at least two pilot scale batches <1> of the medicinal product in the authorized packaging material and/or after the first opening or reconstitution, as appropriate; where applicable, results of appropriate microbiological testing should be included.
2. Revised medicinal product information.
3. Copies of approved end-of-shelf life specifications and, where applicable, specifications after dilution/reconstitution or the first opening (in the form of a link to the relevant document in the dossier sequence or an annex to the cover letter).

4. Justification for the proposed changes.	
<*> Note	Extrapolation not applicable for a biological medicinal product.
<1>	Pilot batches can be accepted with a commitment to verify the shelf life on production batches.

B.II.g) Design space and post-approval change management protocols

B.II.g.3. Deletion of an approved change management protocol related to the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
	1	1, 2	IA_{IN}
Conditions 1. The deletion of the approved change management protocol related to the medicinal 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 marketing authorization application.			
Documentation 1. Justification for the proposed deletion. 2. Amendment of the relevant section(s) of the marketing authorization application.			
B.II.g.4. Changes to an approved change management protocol	Conditions to be fulfilled	Documents and data	Procedure
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. Proof from the marketing authorization holder that any change should be within the range of currently approved acceptance criteria. In addition, proof that an assessment of comparability is not required for biological medicinal products.			
B.II.g.5. Implementation of changes provided for in an approved change management protocol	Conditions to be fulfilled	Documents and data	Procedure

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 medicinal product	-	1, 2, 3, 4, 5	IB
Conditions 1. The proposed change has been performed fully in accordance with the approved change management protocol, which requires immediate notification following implementation.			
Documentation 1. Reference to the approved change management protocol. 2. Proof from the marketing authorization holder that the change is in accordance with the approved change management protocol and that the study results meet the acceptance criteria specified in the protocol. In addition, proof that an assessment of comparability is not required for biological 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 marketing authorization application. 5. Copies of approved specifications of the medicinal product (in the form of a link to the relevant document in the dossier sequence or an annex to the cover letter).			

B.II.h) Adventitious agents safety

B.II.h.1. Update to the information "Adventitious Agents Safety Evaluation (name, dosage form, manufacturer)" (Section 3.2.A.2 of the marketing authorization application)	Conditions to be fulfilled	Documents and data	Procedure
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 marketing authorization application			

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 marketing authorization application, including the introduction of the new studies to investigate the capability of manufacturing steps to inactivate/eliminate adventitious agents. 2. Justification that the studies do not modify the risk assessment. 3. Amendment of product information (where applicable).			

B.III. Certificate of Suitability to the European Pharmacopoeia (CEP) (if any) and/or TSE Certificate of Suitability and/or changes in the active pharmaceutical ingredient and excipients to comply with the Pharmacopoeia of the Union, the pharmacopoeia of a Member State or other pharmacopoeias in accordance with the Concept

B.III.1. Submission of a new or updated Ph. Eur. Certificate of Suitability or deletion of a Ph. Eur. Certificate of Suitability for: an active pharmaceutical ingredient; a starting material/reagent/ intermediate used in the manufacturing process of the active pharmaceutical ingredient; an excipient.	Conditions to be fulfilled	Documents and data	Procedure
a) Certificate of Suitability to the European Pharmacopoeia			
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 pharmaceutical	–	1, 2, 3, 4, 5, 6	IB

ingredient 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			
b) Ph. Eur. TSE Certificate of Suitability for an active pharmaceutical ingredient/starting material/reagent/intermediate/excipient			
1. New certificate for an active pharmaceutical ingredient 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/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. Medicinal product release and end-of-shelf life specifications remain the same.
2. Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with the guidelines of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use) and product specific requirements (e.g. particle size profiles, polymorphic forms), if applicable.
3. The manufacturing process of the active pharmaceutical ingredient, 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 an active pharmaceutical ingredient 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 pharmaceutical ingredient/starting material/reagent/intermediate/ excipient is not sterile.
6. For herbal preparations: the manufacturing route, physical form, extraction solvent and drug extract ratio should remain the same.
7. If gelatine manufactured from bones is to be used in a medicinal product for parenteral use, it should only be manufactured in accordance with the requirements of the manufacturer's country.
8. At least one manufacturer for the same substance remains in the marketing authorization application.
9. If the active pharmaceutical ingredient is a not a sterile substance but is to be used in a sterile medicinal product, then in accordance with the CEP it must not use water during the last steps of the synthesis or, if it does, the active pharmaceutical ingredient 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 and additionally the cover letter should clearly outline the present and proposed manufacturers.
3. Amendment of the relevant section(s) of the marketing authorization application.
4. Where applicable, a document providing information of any materials falling within the scope of the monograph of the Pharmacopoeia of the Union or the European Pharmacopoeia on minimizing 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 pharmaceutical ingredient/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. For an active pharmaceutical ingredient, a declaration by the qualified person of each of the manufacturing authorization holders listed in the application where the active pharmaceutical ingredient is used as a starting material and a declaration by the qualified person of each of the manufacturing authorization holders listed in the application as responsible for batch release. These declarations should state that the active pharmaceutical ingredient manufacturer referred to in the application carries out its activities in accordance with the Rules of Good Manufacturing Practice for starting materials. A single declaration may be acceptable under certain circumstances (see the note under variation B.II.b.1). The manufacture of intermediates also requires a declaration by the qualified person, while as far as any updates to certificates for active pharmaceutical ingredients and intermediates are concerned, a declaration by the qualified person 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 pharmaceutical ingredient with the corresponding requirements on quality of water for pharmaceutical use.

B.III.2. Changes in the active pharmaceutical ingredient or an excipient to comply with the Pharmacopoeia of the Union, the pharmacopoeia of a Member State or other pharmacopoeias in accordance with the Concept	Conditions to be fulfilled	Documents and data	Procedure
a) Change of specification(s) of a former non-pharmacopoeial substance to fully comply with the Pharmacopoeia of the Union or with the pharmacopoeia of a			

Member State			
1. Active pharmaceutical ingredient	1, 2, 3, 4, 5	1, 2, 3, 4	IA_{IN}
2. Excipient/active pharmaceutical ingredient starting material	1, 2, 4	1, 2, 3, 4	IA
b) Changes to comply with an update of the relevant monograph of the Pharmacopoeia of the Union, the pharmacopoeia of a Member State or other pharmacopoeias in accordance with the Concept	1, 2, 4, 5	1, 2, 3, 4	IA
c) Change in specifications from the pharmacopoeia of a Member State to the Pharmacopoeia of the Union	1, 4, 5	1, 2, 3, 4	IA
d) Change to replace the manufacturer's test procedure with the procedures of the Pharmacopoeia of the Union, the pharmacopoeia of a Member State and/or other pharmacopoeias according to the Concept in relation to the active pharmaceutical ingredient, an excipient, starting material and/or primary packaging material		1, 2, 3, 4	IA
e) Change in the classification of an excipient from a "novel excipient" (3.2.P.4.6) to an "excipient according to the Pharmacopoeia of the Union and/or other pharmacopoeias according to the Concept" (3.2.P.4.1)	6, 7, 8, 9, 10	1, 2	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, the polymorphic form or, e.g. bioassays, aggregates). 3. No significant changes in the qualitative and quantitative impurity profile unless the specifications are tightened. 4. Additional validation of a new or changed pharmacopoeial procedure is not required. 5. For herbal preparations: the manufacturing route, physical form, extraction solvent and drug extract ratio should remain the same. 6. An excipient fully complies with the requirements of the monograph in the relevant pharmacopoeia, and all tests comply with pharmacopoeial standards. 7. Additional specification parameters for specific properties are unchanged (e.g. particle size distribution, the polymorphic form or, e.g. bioassays, aggregates). 8. An excipient must remain unchanged. 9. Additional validation of a new or changed pharmacopoeial method is not required. 10. An excipient has already been approved by the authorized authority for use in the medicinal product with a specific route of administration.	
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application. 2. Comparative table of current and proposed specifications. 3. Batch analysis data (in a comparative tabulated format) on at least two production batches of the relevant substance for all tests in the new specification and additionally, where appropriate, comparative dissolution profile data for the medicinal product on at least one pilot batch. For herbal medicinal products, comparative disintegration data may be sufficient. 4. Data to demonstrate the suitability of the monograph to control the substance, e.g. a comparison of the potential impurities with other specified and detectable impurities in the API, a starting material or an excipient.	
Note:	There is no need to notify the authorized authorities of an updated monograph of the Pharmacopoeia of the Union or the pharmacopoeia of a Member State in the case that a specification is introduced under the relevant updated monograph within six months after its publication and reference is made to the “current edition (in accordance with the legislation of a Member State)” in the marketing authorization application for an authorized medicinal product.

B.IV. Medical products (devices and component parts) included in the packaging of the medicinal product

B.IV.1. Change of component parts for measuring, including medical products for administration	Conditions to be fulfilled	Documents and data	Procedure
a) Addition or replacement of devices or component parts, including medical products, which are not an integrated part of the primary packaging			
1. Medical products authorized in accordance with the Rules of Marketing Authorization and Assessment of the Safety, Quality and Efficiency of Medical Products approved by Decision No. 46 of the Eurasian Economic Commission's Council dated February 12, 2016, or in accordance with the legislation of a Member State or authorized for circulation in third countries	1, 2, 3, 5, 6	1, 2, 3	IA_{IN}
2. Medical products (devices and component parts) which may have a significant impact on the delivery of the active substance in the medicinal product (e.g. spacer devices for metered dose inhalers, nebulizers)	–	–	II
b) Deletion or replacement of medical products (devices and component parts) included in the packaging of the medicinal product	4	1, 4	IA_{IN}
c) Addition or replacement of a device or component part which is an integrated part of the primary packaging	–	–	II

Conditions 1. The proposed measuring/administration device must accurately deliver the required dose for the product concerned in line with the approved posology. Results of such studies should be available. 2. The new measuring/administration device is compatible with the medicinal product. 3. The change should not lead to substantial amendments of product information. 4. The medicinal product can still be accurately delivered. 5. The medical product is not used as a solvent of the medicinal product. 6. If the function of accurate measurement is intended, the information on it should be included in the marketing authorization application for the medicinal product.
Documentation 1. Amendment of the relevant section(s) of the marketing authorization application, including the scheme of the component part/medical product, the composition of its materials, the information on the supplier where appropriate, and revised product information as appropriate. 2. Document confirming the marketing authorization of a medical product in the Union or in accordance with the legislation of a Member State or authorization for circulation in third countries (if applicable). 3. Documents and information to demonstrate dosing accuracy and compatibility of the component part or the medical product with the medicinal product. 4. Justification for the deletion or replacement of the medical product (device or component part).

Note:	For B.IV.1.c), any change which results in a new dosage form requires the submission of an extension application.

B.V. Changes to a marketing authorization application 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 application for a medicinal product (PMF 2nd step procedure)	Conditions to be fulfilled	Documents and data	Procedure
a) First-time inclusion of a new Plasma Master File affecting the properties of the medicinal product	-	-	II

b) First-time inclusion of a new Plasma Master File not affecting the properties of the medicinal product	-	1, 2, 3, 4	IB
c) Inclusion of an updated/amended Plasma Master File when changes affect the properties of the medicinal product	-	1, 2, 3, 4	IB
d) Inclusion of an updated/amended Plasma Master File when changes do not affect the properties of the medicinal product	1	1, 2, 3, 4	IA_{IN}
Conditions 1. The updated or amended PMF has been granted the PMF certificate of the Union in accordance with Appendix 1 to the Rules of Marketing Authorization and Assessment.			
Documentation 1. Proof that the PMF certificate of the Union and the assessment report are fully applicable for the authorized product. The PMF holder has provided the PMF certificate of the Union, the assessment report and the PMF dossier to the marketing authorization holder (where the marketing authorization holder is different from the PMF holder). The PMF certificate of the Union and the assessment report replace the previous PMF documentation for this medicinal product. 2. PMF certificate of the Union and assessment report. 3. A declaration by the qualified person that outlines all the changes introduced with the certified PMF and evaluates their potential impact on the medicinal products, including product specific risk assessments. 4. The variation application form should clearly reflect the present and proposed PMF certificate of the Union (code number) in the marketing authorization application. When applicable, the variation application form should clearly list also all the other PMFs to which references are made in the marketing authorization application for the medicinal product even if these PMFs 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 application for a medicinal product (VAMF 2nd step procedure)	Conditions to be fulfilled	Documents and data	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 medicinal 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 medicinal product	1	1, 2, 3, 4	IA_{IN}
Conditions 1. The updated or amended VAMF has been granted the VAMF certificate of the Union in accordance with Appendix 1 to the Rules of Marketing Authorization and Assessment.			
Documentation 1. A declaration that the VAMF certificate of the Union and the assessment report are fully applicable for the authorized product. The VAMF holder has provided the VAMF certificate of the Union, the assessment report and the VAMF dossier to the marketing authorization holder (where the marketing authorization holder is different from the VAMF holder). The VAMF certificate of the Union and the assessment report replace the previous VAMF documentation for this medicinal product. 2. VAMF certificate of the Union and assessment report. 3. A declaration by the qualified person that outlines all the changes introduced with the certified VAMF and evaluates their potential impact on the medicinal products, including product specific risk assessments. 4. The variation application form should clearly reflect the present and proposed VAMF certificate of the Union (code number) in the marketing authorization application. When applicable, the variation application form should clearly list also all the other VAMFs to which references are made in the marketing authorization application for the medicinal product even if these VAMFs are not the subject of the application.			

B.V.b) Updates as a result of requests from authorized authorities (expert organizations), including based on the results of consideration by the Expert Committee

B.V.b.1. Update of the quality dossier intended to implement the opinion or request of the authorized authority (expert	Conditions to be fulfilled	Documents and data	Procedure

organization) (recommendation of the Expert Committee)			
a) The change implements the opinion or request of the authorized authority (expert organization) (recommendation of the Expert Committee)	1	1, 2	IA_{IN}
b) The harmonization of the quality dossier was not part of the opinion or request of the authorized authority (expert organization) (recommendation of the Expert Committee), 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 opinion or request of the authorized authority (expert organization) (recommendation of the Expert Committee). 2. The changes introduced during the procedure of referral to the authorized authority (expert organization) should be clearly highlighted in the submission.			

”;

c) in Section C of the table:

Subsections C.I.1–C.I.8 shall read as follows:

“C.I. Human medicinal products

C.I.1. Change(s) in the summary of product characteristics, packaging mock-ups or the package leaflet intended to implement the requirements specified in the opinion or request of the authorized authority (expert organization)	Conditions to be fulfilled	Documents and data	Procedure
a) The marketing authorization application for the medicinal product is undergoing assessment by the authorized authority (expert organization)	1	1, 2, 3	IA_{IN}
b) The marketing authorization	1	1, 2, 3	IA

application for the medicinal product has not been filed for assessment with the authorized authority (expert organization) but changes implement the requirements specified in the opinion or request of the authorized authority (expert organization) and no new additional data is required to be submitted by the marketing authorization holder			
c) Changes implement the requirements specified in the opinion or request of the authorized authority (expert organization) with new additional data submitted by the marketing authorization holder	-	-	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 opinion or request of the authorized authority (expert organization) with the annexed summary of product characteristics, packaging mock-ups or package leaflet. 2. A declaration that the proposed summary of product characteristics, packaging mock-ups and package leaflet are identical in the concerned sections to those annexed to the opinion or request of the authorized authority (expert organization). 3. Revised medicinal product information.			
C.I.2. Change(s) in the summary of product characteristics, packaging mock-ups or the package leaflet of a generic, hybrid or biosimilar medicinal product following assessment of the same change for the reference medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) Implementation of change(s) for which no new additional data is required to be submitted by the	–	1, 2	IB

marketing authorization holder			
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the marketing authorization holder (e.g. comparability)	–	–	II
Documentation 1. Attached to the cover letter of the variation application: A request of the authorized authority, if applicable. 2. Revised medicinal product information.			
C.I.3. Change(s) in the summary of product characteristics, packaging mock-ups or the package leaflet of human medicinal products intended to implement the outcome of a post-authorization safety study or the conclusion and proposed follow-up actions in a periodic safety update report	Conditions to be fulfilled	Documents and data	Procedure
a) Implementation of wording agreed by the authorized 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 marketing authorization holder	–	–	II
Conditions 1. The variation introduces the wording agreed by the authorized 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 agreement/assessment of the authorized authority. 2. Revised medicinal product information.			
C.I.4. Significant change(s) in the summary of product characteristics because of new quality, preclinical, clinical or	Conditions to be fulfilled	Documents and data	Procedure

pharmacovigilance data			
	–	–	II

Note:	This variation does not apply when the new data has been submitted in accordance with variation C.I.13. In such cases, the change in the summary of product characteristics, packaging mock-ups and/or the package leaflet is classified as variation C.I.13.

C.I.5. Change in the legal status of a medicinal product	Conditions to be fulfilled	Documents and data	Procedure
a) For generic, hybrid or 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 the legal status change of the reference medicinal product (e.g. reference to the decision adopted by the authorized authority of a Member State).
2. Revised medicinal product information.

C.I.6. Change(s) to the therapeutic indication(s) and/or dosage regimen	Conditions to be fulfilled	Documents and data	Procedure
a) Addition of a new therapeutic indication and/or dosage regimen or modification of the approved ones	–	–	II
b) Deletion of a therapeutic indication and/or dosage regimen	–	–	IB

Note	Where the addition or modification of a therapeutic indication and/or dosage regimen takes place in the context of the implementation of the requirements specified in the opinion or request of the authorized authority (expert organization), or – for a generic, hybrid or biosimilar product – when the changes of product information have been made following the assessment of similar changes for the reference medicinal product, such changes are classified as variations C.I.1 and C.I.2, respectively.

C.I.7 Deletion of:	Conditions to be fulfilled	Documents and data	Procedure

a) dosage form	–	1, 2	IB
b) a strength	–	1, 2	IB
Documentation 1. A declaration that the remaining product presentation(s) is (are) adequate for the dosing instructions and treatment duration as described in the summary of product characteristics. 2. Revised medicinal product information.			
Note	In cases where a given dosage form or strength has received a marketing authorization as a separate medicinal product, the deletion of such dosage form or strength will not be a variation but the withdrawal of the marketing authorization.		
C.I.8. Introduction of, or changes to, a summary of the pharmacovigilance system of the marketing authorization holder for the medicinal product for human use <*>	Conditions to be fulfilled	Documents and data	Procedure
a) Introduction of a summary of the pharmacovigilance system of the marketing authorization holder for the medicinal product, changes in the QPPV (including contact information) and/or changes in the Pharmacovigilance System Master File (PSMF) location	-	1, 2	IA_{IN}
Documentation 1. Summary of the pharmacovigilance system of the marketing authorization holder for the medicinal product or update of the relevant elements (as applicable): proof that the applicant has at disposal a QPPV and a statement signed by the applicant to the effect that the applicant has the necessary means to fulfill the tasks and responsibilities listed in the Rules of Good Pharmacovigilance Practice; contact information of the QPPV, the Member State in which the QPPV resides and carries out his/her tasks; PSMF location. 2. PSMF number (if available).			

Subsection C.I.9 shall be invalidated;

Subsections C.I.10–C.I.13 shall read as follows:

“

C.I.10. Change in the frequency and/or date of submission of periodic safety update reports (PSUR) for medicinal products	Conditions to be fulfilled	Documents and data	Procedure
	1	1, 2	IA_{IN}
Conditions 1. The change in the frequency and/or date of submission of the periodic safety update report has been agreed by the authorized authority of a Member State.			
Documentation 1. Attached to the cover letter of the variation application: A reference to the agreement of the authorized authority. 2. Revised frequency and/or date of submission of the periodic safety update report.			
Note	This variation applies only when the submission frequency of periodic safety update reports is specified in the marketing authorization application by other means than a reference to the list of reference dates in accordance with the acts of the Union’s governing bodies in the field of medicines circulation and where the submission of a periodic safety update report 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	Documents and data	Procedure
a) Implementation of wording agreed by the authorized 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 marketing authorization holder where significant assessment by the authorized authority is required <*>	–	–	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 authorized authority.			

2. Revised medicinal product information.			
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 in exceptional cases and conditional marketing authorization.		
<*>	The introduction of a risk management plan requested by the authorized authority always requires significant assessment.		
C.I.12. Inclusion or deletion of the black triangle symbol or explanatory statements for medicinal products that are subject to additional monitoring in accordance with the recommendation of the Expert Committee		Conditions to be fulfilled	Documents and data	Procedure
		1	1, 2	IA_{IN}
Conditions 1. The medicinal product is subject to additional monitoring in accordance with the recommendation of the Expert Committee.				
Documentation 1. Attached to the cover letter of the variation application: A reference to the recommendation of the Expert Committee. 2. Revised medicinal product information.				
Note	This variation covers the situation where the inclusion or deletion of the black triangle symbol or explanatory statements is not performed as part of another regulatory procedure (e.g. the procedure of confirmation (renewal) of the marketing authorization or the variation procedure affecting product information).			

;

the following Subsection C.I.14 shall be added:

“

B.I.14. Clarification of storage conditions during the use of the medicinal product in Section 4.2 of the summary of product characteristics and Section 3 of the package leaflet to ensure proper handling of the medicinal product	Conditions to be fulfilled	Documents and data	Procedure
	–	1, 2, 3	IB

Documentation 1. Amendment of the relevant section(s) of the marketing authorization application. The amendment must contain results of appropriate real-time stability studies (covering the entire shelf life, if applicable) conducted in accordance with the acts of the Union's governing bodies in the field of medicines circulation on at least one pilot scale batch of the medicinal product in the authorized packaging material and/or after the first opening or reconstitution, as appropriate. Where applicable, results of appropriate microbiological testing should be included. 2. Revised medicinal product information. 3. Copies of approved end-of-shelf life specifications and, where applicable, specifications after dilution/reconstitution or the first opening (in the form of a link to the relevant document in the dossier sequence or an annex to the cover letter).

";

d) Section D of the table shall read as follows:

"D. PMF/VAMF

D.1. Change in the name and/or address of the VAMF certificate holder	Conditions to be fulfilled	Documents and data	Procedure
	1	1	IA_{IN}
Conditions 1. The VAMF certificate holder must remain the same juridical person.			
Documentation 1. A formal document from a relevant authorized authority (e.g. a tax authority) 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	Documents and data	Procedure
	1	1	IA_{IN}
Conditions 1. The PMF certificate holder must remain the same juridical person.			
Documentation 1. A formal document from a relevant authorized authority (e.g. a tax authority) 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. a different juridical person	Conditions to be fulfilled	Documents and data	Procedure

	-	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 transaction date – signed by both companies. 2. Copy of the last page in the PMF certificate of the Union. 3. Proof of establishment of the new holder (Excerpt from the register of juridical persons 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 information of the person responsible for communication between the authorized authority and the PMF holder, signed by the transferee. 6. Letter of Undertaking to fulfill 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	Documents and data	Procedure
	1, 2	1, 2, 3	IA
Conditions 1. The blood establishment must remain the same juridical person. 2. The change must be administrative (e.g. merger, take-over); in case of the change in the name of the blood establishment (blood/plasma collection center), its organizational and legal form of ownership, as well as location must remain the same.			
Documentation 1. A signed declaration that the change does not involve a change of the quality system within the blood establishment. 2. A signed declaration that there is no change in the list of the blood/plasma 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	Documents and data	Procedure
	-	1, 2, 3	IB

Documentation
1. Epidemiological data for viral markers related to the blood/plasma collection center covering the last three years. For a newly opened blood/plasma collection center(s) or if no data is yet available, proof that epidemiological data will be provided at the time of the next annual update(s).
2. A statement that the blood/plasma collection center is working under the same conditions as the other centers belonging to the blood establishment, as specified in the standard agreement between the blood establishment and the PMF holder.
3. Updated relevant sections and annexes of the PMF dossier.

D.6. Deletion or change of status (operational/non-operational) of blood establishments (blood/plasma collection centers) used for blood/plasma collection or in the testing of donations and plasma pools	Conditions to be fulfilled	Documents and data	Procedure
	1, 2	1	IA

Conditions
1. The reason for deletion or change of status should not be related to non-compliance with the requirements of the Rules of Good Manufacturing Practice.
2. The blood establishments (blood/plasma collection centers) should comply with the acts of the Union's governing bodies in the field of pharmaceutical inspections and the legislation of the Member State to the extent not regulated by the acts of the Union's governing bodies in case of change of status from non-operational to operational.

Documentation
1. Updated relevant sections and annexes of the PMF dossier.

D.8. Replacement or addition of a blood/plasma collection center for testing of donations and/or plasma pools within a blood establishment already included in the PMF	Conditions to be fulfilled	Documents and data	Procedure
	-	1, 2	IB

Documentation
1. A statement that the testing is performed following the same standard operating procedures and/or test methods as already accepted.
2. Updated relevant sections and annexes of the PMF dossier.

D.10. Replacement or addition of	Conditions to be	Documents	Procedure

a new blood establishment or center in which storage of plasma is carried out	fulfilled	and data	
	–	1, 2	IB
Documentation 1. A statement that the plasma storage center is working in accordance with the same standard operating procedures as the already accepted blood establishment. 2. Updated relevant sections and annexes of the PMF dossier.			
D.11. Deletion of a blood establishment or center in which storage of plasma is carried out	Conditions to be fulfilled	Documents and data	Procedure
	1	1	IA
Condition 1. The reason for deletion should not be related to non-compliance with the requirements of the Rules of Good Manufacturing Practice.			
Documentation 1. Updated relevant sections and annexes of the PMF dossier.			
D.12. Replacement or addition of an organization involved in the transportation of plasma	Conditions to be fulfilled	Documents and data	Procedure
	–	1	IB
Documentation 1. Updated relevant sections and annexes of the PMF dossier, including all the blood establishments using this transportation organization, a summary of the system in place to ensure that the transportation is performed under appropriate conditions (time, temperature and compliance with the Rules of Good Manufacturing Practice) and confirmation that transportation conditions are validated.			
D.13. Deletion of an organization involved in the transportation of plasma	Conditions to be fulfilled	Documents and data	Procedure
	1	1	IA
Condition 1. The reason for deletion should not be related to non-compliance with the Rules of Good Manufacturing Practice.			
Documentation 1. Updated relevant sections and annexes of the PMF dossier.			

D.14. Addition of a test kit authorized in the Union as a medical product to test individual blood and plasma donations as a new test kit	Conditions to be fulfilled	Documents and data	Procedure
	1	1, 2	IA
Conditions 1. The new test kit is authorized in the Union as a medical product.			
Documentation 1. A list of testing sites where the kit is used. 2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing in accordance with the acts of the Union's governing bodies in the field of medicines circulation.			
D.15. Addition of a test kit not authorized in the Union as a medical product to test individual blood and plasma donations as a new test kit	Conditions to be fulfilled	Documents and data	Procedure
a) The new test kit has not previously been approved in the PMF for any blood/plasma collection center for testing of donations	-	-	II
b) The new test kit has been approved in the PMF for other blood/plasma collection centers for testing of donations	-	1, 2	IA
Documentation 1. A list of testing centers where the kit is currently used and a list of testing centers where the kit will be used. 2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing in accordance with the acts of the Union's governing bodies in the field of medicines circulation.			
D.17. Introduction or extension of the quarantine storage procedure	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA
Condition 1. The quarantine storage procedure is a more stringent procedure (e.g. release only after retesting of donors).			

Documentation 1. Updated relevant sections and annexes of the PMF dossier, including the rationale for introduction or extension of the quarantine storage procedure, the sites where quarantine storage takes place and, for changes to the procedure, a decision tree including new conditions.			
D.19. Replacement or addition of blood containers (e.g. bags, bottles)	Conditions to be fulfilled	Documents and data	Procedure
a) The new blood containers are authorized in the Union as medical products	1, 2	1	IA
b) The new blood containers are not authorized in the Union as medical products	-	-	II
Conditions 1. The container is authorized in the Union as a medical product. 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 the container, manufacturer, anticoagulant solution specification, confirmation of marketing authorization in the Union or a Member State and the name of the blood establishments where the container is used.			
D.20. Change in storage/transportation	Conditions to be fulfilled	Documents and data	Procedure
a) storage and/or transportation 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 the requirements of the Pharmacopoeia of the Union or otherwise the pharmacopoeias of the Member States 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 a detailed description of the new conditions, confirmation of validation of storage/transportation conditions and the name of the blood establishment where the change takes place (if relevant).			

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