Republika e Kosovës
Republika Kosova-Republic of Kosova
Qeveria – Vlada – Government

ADMINISTRATIVE INSTRUCTION (HEALTH) NO. 01/2024
VARIATIONS OF MEDICINAL PRODUCTS

Minister of the Ministry of Health,

Pursuant to Article 16, paragraph 3 and 9 of Law No. 04/L-190 on Medicinal Products and Medicinal Devices, (OG no. 27/ 25 April 2014), Article 11, paragraph 1, subparagraph 1.5 of Law No. 08/L-117 on Government of the Republic of Kosovo (OG no. 34 / 18 November 2022), Article 38, paragraph 6 of Regulation No. 09/2011 of Rules and Procedure of the Government of the Republic of Kosovo (OG no. 15 / 12 September 2011), issues the following:

ADMINISTRATIVE INSTRUCTION No. 01/2024 – VARIATIONS OF MEDICINAL PRODUCTS

Article 1
Purpose

1. This Administrative Instruction defines the procedure and conditions for granting approval, acceptance and rejection of variation for all medicinal products with marketing authorization.

2. This Administrative Instruction contains provisions that are partially in accordance with EU Regulation No. 1234/2008 of 24 November 2008.

Article 2
Scope

The provisions of this Administrative Instruction shall apply to the marketing authorization holder or its authorized representative for the application of medicinal product variations.

Article 3
Definitions

1. Expressions, terms and abbreviations used in this administrative instruction have the following meaning:

1.1 Variation - means a change to the contents of the particulars and documents of medicinal products with marketing authorization.

1.2 Minor variation of type IA - means a variation which has only a minimal impact, or no impact at all, on the quality, safety or efficacy of the medicinal product concerned and requires notification from the marketing authorization holder.

1.3 Variation of type IA_{IN} – means a variation that requires notification within 30 days from the date of implementation by the marketing authorization holder.

1.4 Extension – means a variation that fulfils the conditions set in Annex II.

1.5 Major variation of type II - means a variation which is not an extension and which may have a significant impact on the quality, safety or efficacy of the medicinal product in question.

1.6 Minor variation of type IB - means a variation which is neither a minor variation of type IA nor a major variation of type II nor an extension and requires notification from the marketing authorization holder.

1.7 Notifications - means receipt of notifications of type IA, IAIN and IB variations from countries of origin and other countries, except for domestic producers.

2. Expressions, terms and other abbreviations used in this administrative instruction have the meaning as defined by the legislation in force in the field of health.

Article 4
Competent Authority and Responsibilities

Kosovo Medicines Agency is the Competent Authority for the implementation of this Administrative Instruction in accordance with the legislation in force for Medicinal Products and Devices.

Article 5
Classification of variations

1.In relation to any variation that is not an extension, the classification laid down in Annex III shall apply.

2.In cases where the variation is not an extension and whose classification is undetermined according to Annex III of this Instruction, the marketing authorization holder or its authorized representative shall submit a request to the relevant department for evaluation within the KMA.

3.The relevant department, if needed, may request any recommendations in relation to paragraph 2 of this article from the Evaluation Commission for Medical Products and Devices.

4.KMA shall respond to the request in relation to paragraph 3 of this article within 45 days to the applicant.

Article 6
Request for approval/notification of variation

1. The marketing authorization holder or his authorized representative must apply for variation to KMA having the following documents:

   1.1 Application for variation;

   1.2 Cover letter which must contain;

      1.2.1. logo, name and address of the marketing authorization holder;
      1.2.2. subject: description of the submitted variation;
      1.2.3. trade name, INN or generic name, pharmaceutical form, dose;
      1.2.4. packaging of the medicinal product;
      1.2.5. name of the manufacturer;
      1.2.6. date and signature by the person responsible for the documentation of the marketing authorization holder;
      1.2.7 Listing of documents submitted for variation application.

   1.3. Statements about the reasonableness of the grouping of variations.

   1.4. Accompanying documentation related to the applied variation.

   1.5 Proof of payment according to the Administrative Instruction on Fees for services provided in KMA.

2.Variations that have an impact on product information with changes to the summary of product characteristics, label, outer packaging and instruction sheet, marketing authorization holder or the authorized representative is obliged to bring the updated documents in the official languages of the Republic of Kosovo which must be submitted in a cleaned and traceable word version.

Article 7
Group variations

1. The application of group variations is done in the following cases:

   1.1. when the same minor variations of type IA with the same marketing authorization holder are covered only by an application according to article 8 of this instruction;

1.2. an application may cover several variations of a marketing authorization when they are submitted at the same time, provided that the variations in question must comply with one of the points in Annex IV of this Administrative Instruction;

1.3. In cases where the variations do not match in one of the points in Annex IV, the submission of the variations will be done as follows:

1.3.1. a single submission, as referred to in Article 9 of this instruction where at least one of the variations is a minor variation of type IB and all other variations are minor variations:
1.3.2. a single submission, as referred to in Article 10 of this instruction where at least one of the variations is a major type II variation and none of the other variations are extensions;
1.3.3. a single submission as referred to in Article 12 of this guideline, where at least one of the variations is an extension.

2. Submission of group variations can be done up to ten medicinal products within one submission.

Article 8
Notification procedure for Type IA minor variations

1. When the minor IA type variation has been notified in the country of origin or in other countries, the marketing authorization holder or his representative submits to the KMA the notification containing all the points listed in Annex V.

2. The notification is submitted within 12 months from the date of implementation in the above-mentioned countries.

3. In the case of minor IAIN variations, notification is required within 30 days from the marketing authorization holder or his representative after receiving the notification in the country of origin or in other countries for the purpose of continuous supervision of the medicinal product.

4. After receiving the variation notice from the marketing authorization holder or his representative, KMA will review the notice within 60 days for IA and IAIN variations.

Article 9
Procedure for notification of minor variations of type IB

1. When the minor type IB variation has been notified in the country of origin or in other countries, the marketing authorization holder or his authorized representative submits to the KMA the notification containing all the points listed in Annex V.

2. After the notification submission by the marketing authorization holder or his representative, KMA will review the application within 90 days.

3. When KMA rejects the submission for notification of variation, it must notify the marketing authorization holder or his representative of the reasons on which the rejection is based.

4. After the rejection of the notification submission, the holder of the marketing authorization or his representative has the right to re-apply to the KMA.

5. In cases where the request for acceptance of the type IB variation notification is applied as a variation group containing the type II variation, it will be processed according to Article 10 of this administrative instruction.

6. In cases where the request for the acceptance of the notification of variation of type IB is applied as a group of variation containing an extension, it will be processed according to Article 12 of this administrative instruction.

Article 10
Procedure for approval of type II major variations

1. When the major type II variation is approved in the country of origin or in other countries, the marketing authorization holder or his authorized representative submits to the KMA the submission containing all the points listed in Annex V.

2. After receiving the submission for approval of the variation from the marketing authorization holder or its authorized representative, KMA will review the submission within 90 days.

3. Within the term mentioned in paragraph 2 of this article, KMA has the right to request from the holder of the marketing authorization or his representative additional documents in case the need arises, before approving the variation.

4. The marketing authorization holder or its representative is obliged to bring the additional documentation requested by KMA within 15 working days.

5. If the request from paragraph 4 is not fulfilled, the submission is considered rejected.

6. In cases where the request for the approval of the type II variation is applied as a variation group containing an extension, the variation is processed according to Article 12 of this administrative instruction.

7. All type II variations applied according to paragraph 2 of article 6 of this administrative instruction will be sent to the Evaluation Commission for Medical Devices and Products, before their approval.

Article 11
Vaccine variation

1. The variation related to the vaccine is considered a variation according to the points listed in Annex V.

2. In case we are dealing with an annual change of the variation for strains in the vaccine in accordance with WHO recommendations, the marketing authorization holder or its representative submits the request for the approval of the variation according to the points listed in Annex V, for which the KMA decides within 30 days from the date of receipt of the request.

3. In case of declared emergency situation, KMA must accept the variation even without complete documentation according to the approval of the variation by the countries and the procedures mentioned in paragraph 1 article 13 of this Administrative Instruction.

Article 12
Extensions of marketing authorisation

The request for the extension of marketing authorization will be evaluated according to the points listed in Annex II and in case of evaluation for extension, the variation is processed according to the Administrative Instruction for marketing authorization.

Article 13
Simplified procedure for approval/acceptance of notification of variations

1. The marketing authorization holder or its representative for the application of variations of medicinal products that have approval/acceptance of notification of the variation in the countries at the national level in the EU countries and the Schengen area as well as the USA, including the unilateral procedure and the EU Centralized procedure, must complete the following documents:

   1.1. Application of variation;

   1.2. Authorization by the Marketing Authorization Holder;

1.3. Payment slip and proof of payment;

1.4. Approval/acceptance of notification of variation in the above-mentioned places.

2. KMA decides within 30 days to review the applied variation of type IA_{IN}, IA and IB.

3. KMA decides within 60 days to review the type II applied variation.

Article 14
Procedures for notification, approval or rejection of local manufacturer variations

1. The marketing authorization holder or its authorized representative of the local manufacturer shall apply for variation according to these procedures, as follows:

1.1. When the variation is minor of type IA, IA_{IN} or IB, I must notify KMA through the notification application according to Annex V of this administrative instruction.

1.2. When the variation is major type II, it must apply according to Annex V of this administrative instruction:

2. After receiving the application for notification according to paragraph 1.1 of this article, KMA will review the application for variation type IA and IA_{IN} within 30 days.

3. After receiving the application for notification, KMA will review the application for notification for type IB within 30 days.

4. In case of rejection of notification of variation, KMA notifies the bearer or its authorized representative of the reasons on which the rejection is based.

5.After the rejection of the application for notification according to paragraph 4 of this article, the marketing authorization holder or its authorized representative has the right to re-apply to the KMA.

6.After receiving the application for major type II variation from the marketing authorization holder or his authorized representative, KMA will review the application for variation within 60 days.

7.Within the term mentioned in paragraph 6 of this article, KMA has the right to ask the holder of the marketing authorization or his representative for additional documents in case the need arises, before approving the variation.

8. The marketing authorization holder or its representative is obliged to bring the additional documentation requested by KMA within 15 working days.

9. If the request from paragraph 8 is not fulfilled, the application is considered rejected.

10. All type II variations applied according to paragraph 2 of article 6 of this administrative instruction are sent to the Evaluation Commission for Medicinal Devices and Products, before their approval.

11. The application of group variations will be processed according to Article 7 of this administrative instruction.

Article 15
Annexes

1. Annex I, II, III, IV, V, VI are part of this administrative instruction.

1.1 Annex I - APPLICATION.

1.2 Annex II – EXTENSION OF MARKETING AUTHORIZATION.

1.3 Annex III – CLASSIFICATION OF VARIATIONS.

1.4. Annex IV- CASES FOR THE GROUPING OF VARIATIONS.

1.5 Annex V- ELEMENTS TO BE SUBMITTED.

1.6 Annex VI- DOCUMENTATION GUIDLINE BY TYPE OF PROCEDURES FOR APPLICATION OF VARIATIONS OF MEDICINAL PRODUCTS

1. The guideline and the application are updated by the KMA and access will be provided through the KMA website.

Article 16
Repealing provisions

With the entry into force of this administrative instruction, the provisions for variations of Administrative Instructions 17/2013 on Marketing Authorization of Medicinal Products to Be Placed in the Market of the Republic of Kosovo.

Article 17
Transitional provisions

1. All applications that have started the procedures for variations before the entry into force of this administrative instruction are applied the provisions of the Administrative Instruction at the time of starting the application.

2. With the exception of paragraph 1 of this article, for applications that have started the procedures for variations before the entry into force of this Administrative Instruction, the most favourable provisions determined by this Administrative Instruction will be applied.

Article 18
Entry into force

This Administrative Instruction enters into force seven (7) days after publication in the Official Gazette.

Prishtina __/__/2024

Minister of Health

Dr. Arben Vitia

APPLICATION FOR VARIATION TO A MARKETING AUTHORISATION

Variation procedure number: .....

Type of Application (tick all applicable options)

- ☐ **Type IA_{IN}**
- ☐ **Type IA**
- ☐ **Type IB unforeseen**[1]
- ☐ **Type IB**
- ☐ **Type II**
- ☐ **Type II Art. 29**[2]

- ☐ **Single variation**
- ☐ **Grouping of variations**
- ☐ **Worksharing**

Change(s) concern(s) (for Type IB and Type II variations only, tick all changes applicable):

- ☐ **Indication**
- ☐ **Paediatric** **requirements**
- ☐ **Safety**
- ☐ **Following Urgent Safety Restriction**
- ☐ **Quality**
- ☐ **Annual variation for human influenza vaccines**
- ☐ **Non-food producing target species**
- ☐ **Other**

Name and address of the Applicant/MA holder[3]:

Name and address of contact person[4]:

Telephone number:
Fax number (optional):
E-mail:

[1] A variation is considered 'unforeseen' when the proposed variation is not considered a minor variation of Type IB following the Commission Guideline, or has not been classified as a Type IB variation in an Article 5 recommendation. When one or more of the conditions established in the guideline for a Type IA variation are not met, the concerned change may be submitted as a Type IB variation unless the change is specifically classified as a major variation of Type II.
[2] Type II variation submitted under Article 29 of Regulation (EC) No 1901/2006.

[3] For worksharing or grouped variations affecting more than one MA, indicate the MA holder to be used as reference MA holder for the handling of the procedure.
[4] As specified in section 2.4.3 in Part IA/Module 1 Application Form. If different, attach letter of authorisation. For worksharing or grouped variations affecting more than one MA, a single contact should be designated for the application (see also Signatory box below). In case of national marketing authorisations, several contact points in different Member States can be introduced for type II variations and worksharing.

PRODUCTS CONCERNED BY THIS APPLICATION[5]

(Invented)Name(s):	Active substance(s)	Pharmaceutical form	Strength	MA holder name(s):	MA number(s):[6]	MRP Variation Number[6]

[5] If this list is very extensive (more than one page) it may be added as annex to the application form.
For products authorised via the Centralised Procedure, the Annex A of the product(s) concerned should be provided as an Annex to the application form. For worksharing procedures submitted to the EMA, which include nationally authorised products, relevant product and Member State details should be provided as an Annex B to the application form (U*sing the template on the EMA website*).

[6] Indicate the MA numbers affected (a range may be appropriate). For the MRP variation number, which is a product specific number, see the Best Practice Guide on Variations, Chapter 1, example: NL/H/0123/001-004/IB/033/G. For purely nationally authorised products: number to be completed according to requirements of the relevant National Competent Authority

TYPE(S) of CHANGE(S)

☐ Copy of the relevant page(s) from the Guideline for this/these change(s) is attached and the relevant

boxes for conditions and documentation (both for Type IA and Type IB) are ticked

VARIATIONS INCLUDED IN THIS APPLICATION:

Number and title of variation, as per the classification guideline	**Procedure type**
Specific variation applied for, as per the classification guideline	type

***(Select and include** in this section the applicable variation(s) from the list presented at the end of this application form template (see detailed instructions provided with the list). The above example and the list of variations at the end of the form should subsequently be deleted from the completed form to be submitted).*

PRECISE SCOPE AND BACKGROUND FOR CHANGE, AND JUSTIFICATION FOR GROUPING, WORKSHARING AND CLASSIFICATION OF UNFORESEEN CHANGES (if applicable)

(*Include a description and background of all the proposed changes. In case of grouping and worksharing a justification should be provided in a separate paragraph. If a variation concerns an unforeseen change, include a justification for its proposed classification).*

PRESENT [7,8]	PROPOSED [7,8]
D-U-N-S number:[9] EU or National ASMF number:[10]	D-U-N-S number:[9] EU or National ASMF number:[10]

OTHER APPLICATIONS[11]

[7] Specify the precise present and proposed wording or specification, including dossier section number(s) at the lowest possible level.
[8] For SPC, labelling and package leaflet changes, underline or highlight the changed words presented in the table above or provide as a separate Annex
[9] If applicable, include D-U-N-S number. The Data Universal Numbering System (D-U-N-S) is a system developed by Dun & Bradstreet (D&B) which assigns a unique digit numeric identifier to a single business entity. It is used in this case to facilitate the identification of manufacturing sites outside of EEA
[10] If applicable, include EU or National ASMF reference number (only if EU ASMF reference number is not available)
[11] Due to complexity it is not necessary to complete this section for worksharing or grouped variations affecting more than one MA.

Type II variations – Paediatric Requirements:

(For human medicinal products only; section to be completed only for variations concerning a new indication or for variations related to PIP implementation)
(*Note: The notion of 'global marketing authorisation' as stated in Article 6(1)2nd subparagraph of Directive 2001/83/EC, as amended, should be taken into account for products belonging to the same[12] marketing authorisation holder)*

❍ **ARTICLE 8 OF THE PAEDIATRIC REGULATION APPLIES TO THIS VARIATION APPLICATION, SINCE:**

❍ The application relates to a new indication for an authorised medicinal product, which:
- ❍ is protected by a supplementary protection certificate under Regulation (EC) No 469/2009
- ❍ is protected by a patent which qualifies for the granting of the supplementary protection certificate

❍ The application relates to a previous/ongoing/parallel procedure which triggered the Article 8 requirement. Competent authority/EMA procedure number:

❍ **ARTICLE 8 OF THE PAEDIATRIC REGULATION DOES NOT APPLY TO THIS APPLICATION, SINCE:**

- ❍ the authorised medicinal product is not protected by a supplementary protection certificate under Regulation (EC) No 469/2009 or by a patent which qualifies for the granting of the supplementary protection
- ❍ it relates to a well-established use, generic, hybrid, bio-similar marketing authorisations or traditional herbal medicinal products

❍ **THIS APPLICATION RELATES TO A NEW INDICATION FOR A PAEDIATRIC USE MARKETING AUTHORISATION** (PUMA).

☐ **THIS APPLICATION RELATES TO PAEDIATRIC STUDIES SUBMITTED ACCORDING TO ARTICLE 45 OR 46 OF THE PAEDIATRIC REGULATION.**

☐ **THIS APPLICATION RELATES TO PAEDIATRIC STUDIES INCLUDED IN A PAEDIATRIC INVESTIGATION PLAN**

THIS APPLICATION INCLUDES:

❍ PIP[13]

PIP Decision Number(s):

❍ Product-Specific Waiver[14] Waiver Decision Number(s):

❍ Class waiver

Waiver Decision Number(s):

[12] Same" applicant/marketing authorisation holder: as per the Commission Communication (98/C 299/03) (i.e. belonging to the same mother company or group of companies or which are "licencees")
[13] To be ticked when the PIP Opinion includes a waiver
[14] To be ticked only if there is a product-specific waiver opinion covering all the subsets of the paediatric population

(Note: a copy of the PIP/Product-Specific Waiver decision including the Paediatric Committee (PDCO) opinion and the Summary Report, is to be included in Module 1.10)

HAS THIS APPLICATION BEEN SUBJECT TO PIP COMPLIANCE VERIFICATION?

❍ No
❍ Yes

If, yes, please specify the compliance document reference(s):

(Note: If available, a copy of the PDCO compliance report with, where applicable, the PDCO opinion or the document issued by the national competent authority is to be included in Module 1.10)

☐ Please provide the overview table of PIP results in Module 1.10

Type II variations – Extended data exclusivity/market protection:

(Delete this section if not applicable)

CONSIDERATION OF THIS APPLICATION IS ALSO REQUESTED UNDER THE FOLLOWING ARTICLE IN DIRECTIVE 2001/83/EC OR REGULATION (EC) N° 726/2004:

❍ Article 10(1) of Directive 2001/83/EC / Article 14(11) of Regulation (EC) No 726/2004 (one year of market protection for a new indication)

❍ Article 10(5) of Directive 2001/83/EC (one year of data exclusivity for a new indication)

❍ Article 74(a) of Directive 2001/83/EC (one year of data exclusivity for a change in classification)

(Note: The report justifying the claim for extended data exclusivity/market protection is to be provided in Module 1.5.3)

The following amended product information proposals are provided in the relevant sections of the EU-CTD format or NTA volume 6B format, where applicable:

☐ Summary of Product Characteristics
☐ Manufacturing Authorisation Holder responsible for batch release and conditions of the Marketing Authorisation[15]

☐ Labelling

[15] only for centrally authorised products (Annex II of the EU MA)

☐ Package leaflet
☐ Mock-ups[16]
☐ Specimens[16]

Declaration of the Applicant:

I hereby submit a notification/application for the above Marketing Authorisation(s) to be varied in accordance with the proposals given above. I declare that (*Please tick the appropriate declarations*):

- ☐ There are no other changes than those identified in this application (except for those addressed in other variations submitted in parallel);
- ☐ Where applicable, all conditions as set for the variation(s) concerned are fulfilled;
- ☐ For type IA notifications: the required documents as specified for the changes concerned have been submitted; ☐ Where applicable, national fees have been prepaid or will be paid in accordance with national requirements;
- ☐ This notification/application has been submitted simultaneously in RMS and all CMSs *(for products within the Mutual Recognition Procedure and worksharing)* or both to EMA and (Co-) Rapporteur *(for products within the Centralised Procedure) or, in case of worksharing involving the EMA, to the relevant National Competent Authorities and/or RMS/CMS (as applicable) and the EMA;*
- ☐ For worksharing or grouped variations affecting more than one MA: the MAs concerned belong to the same MAH.

Change(s) will be implemented from[17]: ☐ Next production run/next printing
☐ Date: _____

[16] see Chapter 7 of Volume 6A of the Notice to Applicants or Transfer of information contained in Notice to Applicants, Volume 2A, Chapter 7 (http://www.hma.eu) or Dossier requirements for Centrally Authorised Products (http://www.ema.europa.eu)

[17] Only to be completed for Type IB and Type II variations.

☐ **Proof of payment (when relevant)**

Have all relevant fees been prepaid to competent authorities?

❍ Yes (for fees paid, attach proof of payment in Annex)

Please specify fee category under National rules:

❍ No

For Member State(s):

Please specify the reasons according to National requirements (exemption or later payment).

☐ **Billing address (when relevant)**

Company name:

VAT number:

Address:

Postcode:

Country:

Telephone:

Telefax (optional):

E-Mail:

Purchase order (PO) number:

Main Signatory[18] Status (Job title)

_____ _____

Print name Date

_____ _____

☐ For worksharing/grouping for more than one MA: the main signatory confirms authorisation to sign on behalf of the designated contacts as specified in section 2.4.3 in Part IA/Module 1 Application Form for each of the MAs concerned.

Second Signatory

_____

Print name Status (Job title)

_____ _____

Date

_____

[18] The main signatory is mandatory

LIST OF VARIATIONS (to be deleted upon completion of the form**)**

Please select the applicable variation(s) from the list presented below and include in the section "Type(s) of Change(s) – Variations included in this application " above, in accordance with the following instructions:

Only the main header of the change with the variation applied for needs to be included. To apply for variations not foreseen in the guideline, MAHs should declare such other variation ("z") under the specific guideline section concerned at the lowest possible level i.e. either within a specific variation or under the appropriate guideline section title, as appropriate, including its proposed classification. Please indicate whether the variation has been subject to an Article 5 procedure. Examples of such z) variations have been already included in a number of relevant variations and section titles, for convenience.

For Type IA variations the date of implementation by the MAH needs to be added in the last column.

Full details on the precise scope of the variation concerned, should be given in the section 'precise scope' of the application form.

Examples of how the variation(s) should be presented in the section "Type(s) of Change(s)" of the application form.

E.g. when applying for a change outside the approved specification limits for the active substance:

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance	**Procedure type**
Change outside the approved specifications limits range for the active substance	II

E.g. when applying for an 'unforeseen' change concerning specification limits for the active substance:

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance	**Procedure type**
Other variation	.1.1.1.1.1.1 ☐*IA* ☒*IB* ☐*II*

E.g. when applying for an 'unforeseen' change concerning the control of active substance:

B.I.b Change in control of the active substance	Procedure type
Other variation	.1.1.1.1.1.2 ☐*IA* ☒*IB* ☐*II*

The full list of variations is to be deleted from the actual submitted application form.

A. Administrative change	Procedure type
Other variation	.1.1.1.1.1.3 ☐*IA* ☐*IB* ☐*II*

	Procedure type	
Change in the name and/or address of the marketing authorisation holder		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

A.2 Change in the (invented) name of the medicinal product	Procedure type	
for Centrally Authorised products		☐IB¤
for Nationally Authorised Products	1.1.1.1.1.1.1.4 *IB*	

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type	
Change in name of the active substance or of an excipient		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type

5 ***Change in the name and/or address of a manufacturer (including where relevant quality control testing sites); or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel excipient (where specified in the technical dossier)***		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

A.5 Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites)	**Procedure type**	
The activities for which the manufacturer/importer is responsible include batch release		☐IB¤
The activities for which the manufacturer/importer is responsible do not include batch release		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type	
6 ***Change in ATC Code / ATC Vet Code***		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type	
7 ***Deletion of manufacturing sites for an active substance, intermediate or finished product, 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 dossier)****		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

*Note: Where notice has been given by the authorities of the intention to perform an inspection, the deletion of the relevant site shall be notified inmediatly.

	Procedure type

	Changes to date of the audit to verify GMP compliance of the manufacturer of the active substance*	☐IA

B.I ACTIVE SUBSTANCE	Procedure type
Other variation	1.1.1.1.1.1.8 ☐IA ☐IB ☐II

B.I.a Change in manufacture of the active substance	Procedure type
Other variation	1.1.1.1.1.1.9 ☐IA ☐IB ☐II

B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	Procedure type	
The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer.		☐IB¤
Introduction of a manufacturer of the active substance supported by an ASMF	1.1.1.1.1.1.10	II
The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability	1.1.1.1.1.1.11	II
New manufacturer of material for which an assessment is required of viral safety and/or TSE risk	1.1.1.1.1.1.12	II
The change relates to a biological active substance or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product	1.1.1.1.1.1.13	II
Changes to quality control testing arrangements for the active substance-replacement or addition of a site where batch control/testing takes place		☐IB¤
Introduction of a new manufacturer of the active substance that is not supported by an ASMF and requires significant update to the relevant active substance section of the dossier	II	
Addition of an alternative sterilisation site for the active substance using a Ph.Eur. method	IB	

	Introduction of a new site of micronisation	14 *IA*	*.1.1.1.15* ☐*IB*¤
	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	1.1.1.1.1.1.16 *II*	
	New storage site of Master Cell Bank and/or Working Cell Banks	.1.1.1.1.1.1.17 *IB*	
	Other variation	.1.1.1.18 ☐*IA* ☐*IB* ☐*II*	

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.a.2 Changes in the manufacturing process of the active substance		**Procedure type**
	Minor change in the manufacturing process of the active substance	☐IB¤
	Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product.	1.1.1.1.1.1.19 *II*
	The change refers to a biological / immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological substance, which may have a significant impact on the quality, safety and efficacy of the medicinal product and is not related to a protocol	1.1.1.1.1.1.20 *II*

	The change relates to a herbal medicinal product and there is a change to any of the following: geographical source, manufacturing route or production	1.1.1.1.1.1.1.21 *II*
	Minor change to the restricted part of an Active Substance Master File	.1.1.1.1.1.1.22 *IB*
	Other variation	.1.1.1.23 ☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance		**Procedure type**
	Up to 10-fold increase compared to the originally approved batch size	☐IB¤
	Downscaling down to 10-fold	☐IB¤
	The change requires assessment of the comparability of a biological/immunological active substance	1.1.1.1.1.1.1.24 *II*
	More than 10-fold increase compared to the originally approved batch size	1.1.1.1.1.1.1.25 *IB*
	The scale for a biological/immunological active substance is increased / decreased without process change (e.g. duplication of line)	1.1.1.1.1.1.1.26 *IB*
	Other variation	27 ☐*IA* ☐*IB* ☐*II*

¤If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance		**Procedure type**
	Tightening of in-process limits	☐IB¤
	Addition of a new in-process test and limits	☐IB¤
	Deletion of a non-significant in-process test	☐IB¤
	Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the active substance	1.1.1.1.1.1.1.28 *II*

	Deletion of an in-process test which may have a significant effect on the overall quality of the active substance	1.1.1.1.1.1.1.29 *II*
	Addition or replacement of an in-process test as a result of a safety or quality issue	1.1.1.1.1.1.1.30 *IB*
	Other variation	31 ☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.a.5 Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza		**Procedure type**
	Replacement of the strain(s) in a seasonal, pre-pandemic or a pandemic vaccine against human influenza	**1.1.1.1.1.1.1.32** *II*

B.I.b Change in control of the active substance	Procedure type
Other variation	1.1.1.1.33 ☐*IA* ☐*IB* ☐*II*

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance	Procedure type	
Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release		☐IB¤
Tightening of specification limits		☐IB¤
Addition of a new specification parameter to the specification with its corresponding test method		☐IB¤
Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)		☐IB¤
Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product	II	
Change outside the approved specifications limits range for the active substance	II	
Widening of the approved specifications limits for starting materials/intermediates, which may have a significant effect on the overall quality of the active substance and/or the finished product	II	
Addition or replacement (excluding biological or immunological substance) of a specification parameter with its corresponding test method as a result of a safety or quality issue	IB	
Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the active substance, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country	IB	
Other variation	.1.1.1.34 ☐*IA* ☐*IB* ☐*II*	

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.b.2 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance	**Procedure type**	
Minor changes to an approved test procedure		☐IB¤
Deletion of a test procedure for the active substance or a starting material/reagent/ intermediate, if an alternative test procedure is already authorised.		☐IB¤
Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance		☐IB¤
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	
Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate	IB	

¤If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.c Change in container closure system of the active substance	Procedure type
Other variation	1.1.1.1.35 ☐*IA* ☐*IB* ☐*II*

B.I.c.1 Change in immediate packaging of the active substance	Procedure type	
Qualitative and/or quantitative composition		☐IB¤
Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances	II	
Liquid active substances (non sterile)	IB	
Other variation	..1.1.1.36 ☐*IA* ☐*IB* ☐*II*	

¤If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.c.2 Change in the specification parameters and/or limits of the immediate packaging of the active substance	Procedure type	
Tightening of specification limits		☐IB¤
Addition of a new specification parameter to the specification with its corresponding test method		☐IB¤
Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)		☐IB¤
Addition or replacement of a specification parameter as a result of a safety or quality issue	IB	
Other variation	..1.1.1.37 ☐*IA* ☐*IB* ☐*II*	

¤If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.c.3 Change in test procedure for the immediate packaging of the active substance	Procedure type

Minor changes to an approved test procedure		☐IB¤
Other changes to a test procedure (including replacement or addition)		☐IB¤
Deletion of a test procedure if an alternative test procedure is already authorised		☐IB¤

¤If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.d.1 Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier	Procedure type	
Re-test period/storage period		
Reduction		☐IB¤
Extension of the retest period based on extrapolation of stability data not in accordance with ICH/VICH guidelines*	II	
Extension of storage period of a biological/ immunological active substance not in accordance with an approved stability protocol	II	
Extension or introduction of a re-test period/storage period supported by real time data	IB	
Storage conditions		
Change to more restrictive storage conditions of the active substance		☐IB¤
Change in storage conditions of biological/ immunological active substances, when the stability studies have not been performed in accordance with a currently approved stability protocol	II	
Change in storage conditions of the active substance	IB	
Change to an approved stability protocol	38 *IA*	*.1.1.1.39* ☐*IB*¤
Other variation	.1.1.1.40	☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.e.1 Introduction of a new design space or extension of an approved design space for the active substance, concerning:	Procedure type
One unit operation in the manufacturing process of the active substance including the resulting in-process controls and/or test procedures	II
Test procedures for starting materials/reagents/ intermediates and/or the active substance	II

	Procedure type
B.I.e.2 Introduction of a post approval change management protocol related to the active substance	II

	Procedure type	
B.I.e.3 Deletion of an approved change management protocol related to the active substance		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.I.e.4 Changes to an approved change management protocol	Procedure type
Major changes to an approved change management protocol	II
Minor changes to an approved change management protocol that do not change the strategy defined in the protocol	IB
Other variation	..1.1.1.41 ☐*IA* ☐*IB* ☐*II*

B.I.e.5 Implementation of changes foreseen in an approved change management protocol	Procedure type	
The implementation of the change requires no further supportive data		☐IB¤
The implementation of the change requires further supportive data	IB	
Implementation of a change for a biological/immunological medicinal product	IB	

Other variation	..1.1.1.42 ☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II FINISHED PRODUCT	Procedure type
Other variation	1.1.1.1.43 ☐*IA* ☐*IB* ☐*II*

B.II.a Change in description and composition of the Finished Product	Procedure type
Other variation	.1.1.1.44 ☐*IA* ☐*IB* ☐*II*

B.II.a.1 Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking.	Procedure type	
Changes in imprints, bossing or other markings		☐IB¤
Changes in scoring/break lines intended to divide into equal doses	IB	
Other variation	.1.1.1.45 ☐*IA* ☐*IB* ☐*II*	

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.a.2 Change in the shape or dimensions of the pharmaceutical form	Procedure type	
Immediate release tablets, capsules, suppositories and pessaries		☐IB¤
Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses	IB	
Addition of a new kit for a radiopharmaceutical preparation with another fill volume	II	
Other variation	.1.1.1.46 ☐*IA* ☐*IB* ☐*II*	

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.a.3 Changes in the composition (excipients) of the finished product		Procedure type
Changes in components of the flavouring or colouring system		
Addition , deletion or replacement		☐IB¤
Increase or reduction		☐IB¤
Biological veterinary medicinal products for oral use for which the colouring or flavouring agent is important for the uptake by target animal species		II
Other excipients		
Any minor adjustment of the quantitative composition of the finished product with respect to excipients		☐IB¤
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
Change that relates to a biological/immunological product		II
Any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk		II
Change that is supported by a bioequivalence study		II
Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level		IB
Other variation		..1.1.1.47 ☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.a.4 Change in coating weight of oral dosage forms or change in weight of capsule shells	Procedure type	
Solid oral pharmaceutical forms		☐IB¤
Gastro-resistant, modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism	II	
Other variation	..1.1.1.48	☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type
B.II.a.5 Change in concentration of a single-dose, total use parenteral product, where the amount of active substance per unit dose (i.e. the strength) remains the same	II

	Procedure type
B.II.a.6 Deletion of the solvent / diluent container from the pack	IB

B.II.b Change in manufacture of the Finished Product	Procedure type
Other variation	1.1.1.1.49 ☐*IA* ☐*IB* ☐*II*

B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	Procedure type	
Secondary packaging site		☐IB¤
Primary packaging site		☐IB¤
Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/ immunological medicinal products or for pharmaceutical forms manufactured by complex manufacturing processes	II	
Site which requires an initial or product specific inspection	II	
Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products	IB	
Site where any manufacturing operation(s) take plac except batch release, batch control, and seconda packaging, for sterile medicinal products (including tho that are aseptically manufactured) excluding biologic immunological medicinal products	IB	
Other variation	..1.1.1.50 ☐*IA* ☐*IB* ☐*II*	

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product	Procedure type	
Replacement or addition of a site where batch control/testing takes place		☐IB¤
Replacement or addition of a site where batch control/testing takes place for a biological/immunological product and any of the test	II	

	methods performed at the site is a biological/immunological method		
	Replacement or addition of a manufacturer responsible for importation and/or batch release		
	Not including batch control/testing		☐IB¤
	Including batch control/testing		☐IB¤
	Including batch control/testing for a biological/immunol. product and any of the test methods performed at that site is a biological/immunol./immunochemical method	II	
	Other variation	..1.1.1.51	☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.b.3 Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product	**Procedure type**	
Minor change in the manufacturing process		☐IB¤
Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	II	
The product is a biological/immunological medicinal product and the change requires an assessment of comparability	II	
Introduction of a non-standard terminal sterilisation method	II	
Introduction or increase in the overage that is used for the active substance	II	
Minor change in the manufacturing process of an aqueous oral suspension	IB	
Other variation	..1.1.1.52	☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.b.4 Change in the batch size (including batch size ranges) of the finished product		**Procedure type**
Up to 10-fold compared to the originally approved batch size		☐IB¤
Downscaling down to 10-fold		☐IB¤
The change requires assessment of the comparability of a biological/immunological medicinal product or the change in batch size requires a new bioequivalence study		II
The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes		II
More than 10-fold increase compared to the originally approved batch size for immediate release (oral) pharmaceutical forms		IB
The scale for a biological/immunological medicinal product is increased / decreased without process change (e.g. duplication of line)		IB
Other variation	..1.1.1.53	☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product		**Procedure type**
Tightening of in-process limits		☐IB¤
Addition of a new test(s) and limits		☐IB¤
Deletion of a non-significant in-process test		☐IB¤
Deletion of an in-process test which may have a significant effect on the overall quality of the finished product		II
Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product		II

	Addition or replacement of an in-process test as a result of a safety or quality issue	IB
	Other variation	..1.1.1.54 ☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.c Change in control of excipients in the Finished Product	Procedure type
Other variation	1.1.1.1.55 ☐*IA* ☐*IB* ☐*II*

B.II.c.1 Change in the specification parameters and/or limits of an excipient		Procedure type
Tightening of specification limits		☐IB¤
Addition of a new specification parameter to the specification with its corresponding test method		☐IB¤
Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)		☐IB¤
Change outside the approved specifications limits range	II	
Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	II	
Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method, as a result of a safety or quality issue	IB	
Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the excipient, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country	IB	
Other variation	..1.1.1.56 ☐*IA* ☐*IB* ☐*II*	

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.c.2 Change in test procedure for an excipient		Procedure type
Minor changes to an approved test procedure		☐IB¤
Deletion of a test procedure if an alternative test procedure is already authorised		☐IB¤
Substantial change to or replacement of a biological/ immunological/ immunochemical test method or a method using a biological reagent	II	

Other changes to a test procedure (including replacement or addition)	IB

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.c.3 Change in source of an excipient or reagent with TSE risk	**Procedure type**	
From TSE risk material to vegetable or synthetic origin		
For excipients or reagents not used in the manufacture of a biological / immunological active substance or in a biological / immunological medicinal product		☐IB¤
For excipients or reagents used in the manufacture of a biological / immunological active substance or in a biological / immunological medicinal product	IB	
Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by a TSE certificate of suitability	II	

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.c.4 Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier) or a novel excipient	**Procedure type**	
Minor change in synthesis or recovery of a non-pharmacopoeial excipient or a novel excipient		☐IB¤
The specifications are affected or there is a change in physico-chemical properties of the excipient which may affect the quality of the finished product.	II	
The excipient is a biological/immunological substance	II	
Other variation	..1.1.1.57	☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.d Change in control of the Finished Product	**Procedure type**
Other variation	1.1.1.1.58 ☐*IA* ☐*IB* ☐*II*

B.II.d.1 Change in the specification parameters and/or limits of the finished product	Procedure type	
Tightening of specification limits		☐IB¤
Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release		☐IB¤
Addition of a new specification parameter to the specification with its corresponding test method		☐IB¤
Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material)		☐IB¤
Change outside the approved specifications limits range	II	
Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	II	
Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method as a result of a safety or quality issue	IB	
Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur for the finished product*		☐IB¤
Ph. Eur. 2.9.40 Uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 (Uniformity of mass). or Ph. Eur. 2.9.6 (Uniformity of content)		☐IB¤
Other variation	..1.1.1.59	☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.d.2 Change in test procedure for the finished product	Procedure type	
Minor changes to an approved test procedure		☐IB¤

	Deletion of a test procedure if an alternative method is already authorised		☐IB¤
	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	
	Other changes to a test procedure (including replacement or addition)	IB	
	Update of the test procedure to comply with the updated general monograph in the Ph. Eur.		☐IB¤
	To reflect compliance with the Ph.Eur. and remove reference to the outdated internal test method and test method number*		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type
B.II.d.3 Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product	II

B.II.e Change in container closure system of the Finished Product	Procedure type
Other variation	1.1.1.1.60 ☐*IA* ☐*IB* ☐*II*

B.II.e.1 Change in immediate packaging of the finished product	Procedure type	
Qualitative and quantitative composition		
Solid pharmaceutical forms		☐IB¤
Semi-solid and non-sterile liquid pharmaceutical forms	IB	
Sterile medicinal products and biological/ immunological medicinal products.	II	
The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.	II	
Change in type of container or addition of a new container	1.1.1.1.1.1.1.61	
Solid, semi-solid and non-sterile liquid pharmaceutical forms	IB	
Sterile medicinal products and biological/ immunological medicinal products	II	
Deletion of an immediate packaging container that does not lead to the complete deletion of a strength or pharmaceutical form		☐IB¤
Other variation	.1.1.1.62 ☐*IA* ☐*IB* ☐*II*	

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.e.2 Change in the specification parameters and/or limits of the immediate packaging of the finished product	Procedure type	
Tightening of specification limits		☐IB¤
Addition of a new specification parameter to the specification with its corresponding test method		☐IB¤
Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)		☐IB¤

	Addition or replacement of a specification parameter as a result of a safety or quality issue	IB
	Other variation	..1.1.1.63 ☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.e.3 Change in test procedure for the immediate packaging of the finished product		**Procedure type**
	Minor changes to an approved test procedure	☐IB¤
	Other changes to a test procedure (including replacement or addition)	☐IB¤
	Deletion of a test procedure if an alternative test procedure is already authorised	☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging)		**Procedure type**
	Non-sterile medicinal products	☐IB¤
	The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product	II
	Sterile medicinal products	IB

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.e.5 Change in pack size of the finished product	**Procedure type**
Change in the number of units (e.g. tablets, ampoules, etc.) in a pack	

Change within the range of the currently approved pack sizes		☐IB¤
Change outside the range of the currently approved pack sizes	IB	
Deletion of pack size(s)		☐IB¤
Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/ immunological medicinal products.	II	
Change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) products	IB	
Other variation	.1.1.1.64	☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.e.6 Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used))	**Procedure type**	
Change that affects the product information		☐IB¤
Change that does not affect the product information		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.e.7 Change in supplier of packaging components or devices (when mentioned in the dossier)	**Procedure type**	
Deletion of a supplier		☐IB¤
Replacement or addition of a supplier		☐IB¤
Any change to suppliers of spacer devices for metered dose inhalers	II	

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.f.1 Change in the shelf-life or storage conditions of the finished product		Procedure type
Reduction of the shelf life of the finished product		
As packaged for sale		☐IB¤
After first opening		☐IB¤
After dilution or reconstitution		☐IB¤
Extension of the shelf life of the finished product	1.1.1.1.1.1.1.65	
As packaged for sale (supported by real time data)	IB	
After first opening (supported by real time data)	IB	
After dilution or reconstitution (supported by real time data)	IB	
Extension of the shelf-life based on extrapolation of stability data not in accordance with ICH/VICH guidelines*	II	
Extension of the shelf-life of a biological/ immunological medicinal product in accordance with an approved stability protocol.	IB	
Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	II	
Change in storage conditions of the finished product or the diluted/reconstituted product	IB	
Change to an approved stability protocol		☐IB¤
Other variation	..1.1.1.66	☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product, concerning:	Procedure type
One or more unit operations in the manufacturing process of the finished product including the resulting in-process controls and/or test procedures	II
Test procedures for excipients / intermediates and/or the finished product.	II

	Procedure type
B.II.g.2 Introduction of a post approval change management protocol related to the finished product	II

		Procedure type
B.II.g.3 Deletion of an approved change management protocol related to the finished product		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.g.4 Changes to an approved change management protocol	Procedure type
Major changes to an approved change management protocol	II
Minor changes to an approved change management protocol that do not change the strategy defined in the protocol	IB
Other variation	..1.1.1.67 ☐*IA* ☐*IB* ☐*II*

B.II.g.5 Implementation of changes foreseen in an approved change management protocol		Procedure type
The implementation of the change requires no further supportive data		☐IB¤
The implementation of the change requires further supportive data	IB	
Implementation of a change for a biological/immunological medicinal product	IB	

Other variation	..1.1.1.68 ☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.II.h.1 Update to the "Adventitious Agents Safety Evaluation" information (section 3.2.A.2)	**Procedure type**
Studies related to manufacturing steps investigated for the first time for one or more adventitious agents	II
Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier	
1) with modification of risk assessment	II
2) without modification of risk assessment	IB

B.III.1 Submission of a new or updated Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: **- For an active substance** **- For a starting material/reagent/intermediate used in the manufacturing process of the active substance** **- For an excipient**		**Procedure type**
European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.		
New certificate from an already approved manufacturer		☐IB¤
Updated certificate from an already approved manufacturer		☐IB¤
New certificate from a new manufacturer (replacement or addition)		☐IB¤
Deletion of certificates (in case multiple certificates exist per material)		☐IB¤
New certificate for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free		IB
European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient		1.1.1.1.1.1.1.69
New certificate for an active substance from a new or an already approved manufacturer		☐IB¤
New certificate for a starting material/reagent/ intermediate/or excipient from a new or an already approved manufacturer		☐IB¤
Updated certificate from an already approved manufacturer		☐IB¤
Deletion of certificates (in case multiple certificates exist per material)		☐IB¤

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
Other variation	..1.1.1.70 ☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State	**Procedure type**	
Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State		
Active substance		☐IB¤
Excipient/active substance starting material		☐IB¤
Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State		☐IB¤
Change in specifications from a national pharmacopoeia of a Member State to the Ph. Eur.		☐IB¤
Other variation	☐IA ☐IB ☐II	

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.IV Change in Medical Devices	Procedure type
Other variation	1.1.1.1.71 ☐*IA* ☐*IB* ☐*II*

B.IV.1 Change of a measuring or administration device		Procedure type
Addition or replacement of a device which is not an integrated part of the primary packaging		
Device with CE marking		☐IB¤
Device without CE marking (for veterinary products only)	IB	
Spacer device for metered dose inhalers or other device which may have a significant impact on the delivery of the active substance in the product (e.g. nebuliser)	II	
Deletion of a device		☐IB¤
Addition or replacement of a device which is an integrated part of the primary packaging	II	

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.IV.2 Change in specification parameters and/or limits of a measuring or administration device for veterinary medicinal products		Procedure type
Tightening of specification limits		☐IB¤
Addition of a new specification parameter to the specification with its corresponding test method		☐IB¤
Widening of the approved specifications limits, which has a significant effect on the overall quality of the device	II	
Deletion of a specification parameter that has a significant effect on the overall quality of the device	II	
Addition of a specification parameter as a result of a safety or quality issue	IB	

Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)		☐IB¤
Other variation	..1.1.1.72	☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.IV.3 Change in test procedure of a measuring or administration device for veterinary medicinal products	**Procedure type**	
Minor change to an approved test procedure		☐IB¤
Other changes to a test procedure (including replacement or addition)		☐IB¤
Deletion of a test procedure if an alternative test procedure is already authorised		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.V.a.1 Inclusion of a new, updated or amended Plasma Master File in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure)	Procedure type	
First-time inclusion of a new Plasma Master File affecting the properties of the finished product	II	
First-time inclusion of a new Plasma Master File not affecting the properties of the finished product	IB	
Inclusion of an updated/amended Plasma Master File when changes affect the properties of the finished product	IB	
Inclusion of an updated/amended Plasma Master File when changes do not affect the properties of the finished product		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.V.a.2 Inclusion of a new, updated or amended Vaccine Antigen Master File in the marketing authorisation dossier of a medicinal product. (VAMF 2nd step procedure)	Procedure type	
First-time inclusion of a new Vaccine Antigen Master File	II	
Inclusion of an updated/amended Vaccine Antigen Master File, when changes affect the properties of the finished product	IB	
Inclusion of an updated/amended Vaccine Antigen Master File, when changes do not affect the properties of the finished product		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

B.V.b.1 Update of the quality dossier intended to implement the outcome of a Union referral procedure	Procedure type	
The change implements the outcome of the referral*		☐IB¤
The harmonisation of the quality dossier was not part of the referral and the update is intended to harmonise it	II	

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

C.I Changes (Safety/Efficacy) to Human and Veterinary Medicinal Products	**Procedure type**
Other variation	L.1.1.1.73 ☐*IA* ☐*IB* ☐*II*

C.I.1 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure	**Procedure type**	
The medicinal product is covered by the defined scope of the procedure		☐IB¤
The medicinal product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure and no new additional data is required to be submitted by the MAH	IB	
The medicinal product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure with new additional data submitted by the MAH	II	

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

C.I.2 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product	**Procedure type**
Implementation of change(s) for which no new additional data is required to be submitted by the MAH	IB
Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH (e.g. comparability)	II

C.I.3 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006	**Procedure type**	
Implementation of wording agreed by the competent authority		☐IB¤

Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH	II
Other variation	..1.1.1.74 ☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type
C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	II

C.I.5 Change in the legal status of a medicinal product for centrally authorised products	**Procedure type**
For generic/hybrid/biosimilar medicinal products following an approved legal status change of the reference medicinal product	IB
All other legal status changes	II

C.I.6 Change(s) to therapeutic indication(s)	**Procedure type**
Addition of a new therapeutic indication or modification of an approved one	II
Deletion of a therapeutic indication	IB

C.I.7 Deletion of:	**Procedure type**
a pharmaceutical form	IB
a strength	IB

C.I.8 Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use*	**Procedure type**

Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

C.I.9 Change(s) to an existing pharmacovigilance system as described in the detailed description of the pharmacovigilance system (DDPS)	**Procedure type**	
Change in the QPPV and/or QPPV contact details and/or back-up procedure		☐IB¤
Change(s) in the safety database and/or major contractual arrangements for the fulfilment of pharmacovigilance obligations, and /or change of the site undergoing pharmacovigilance activities		☐IB¤
Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system (e.g. change of the major storage/archiving location, administrative changes		☐IB¤
Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH		☐IB¤
Other variation	.1.1.1.75	☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type	
C.I.10 Change in the frequency and/or date of submission of periodic safety update reports (PSUR) for human medicinal products		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

C.I.11 Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan	Procedure type	
Implementation of wording agreed by the competent authority		☐IB¤
Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the competent authority is required*	II	
Other variation	.1.1.1.76	☐*IA* ☐*IB* ☐*II*

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type	
C.I.12 Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type
C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority*	II

C.II Changes to Veterinary medicinal products	Procedure type
Other variation	1.1.1.1.77 ☐*IA* ☐*IB* ☐*II*

	Procedure type
C.II.1 Variations concerning a change to or addition of a non-food producing target species.	II

C.II.2 Deletion of a food producing or non-food producing target species.	**Procedure type**
Deletion as a result of a safety issue	II
Deletion not resulting from a safety issue	IB

	Procedure type
C.II.3 Changes to the withdrawal period for a veterinary medicinal product	II

	Procedure type
C.II.4 Variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue.	II

	Procedure type
C.II.5 Variations concerning the replacement of a strain for a veterinary vaccine against equine influenza	II

	Procedure type
C.II.6 Changes to the labelling or the package leaflet which are not connected with the summary of product characteristics.	IB
a) Administrative information concerning the holder's representative	☐IA_{IN}
b) Other changes	IB

C.II.7 Introduction of a new Pharmacovigilance system	Procedure type

Which has not been assessed by the relevant national competent authority/EMA for another product of the same MAH	II
Which has been assessed by the relevant national competent authority/EMA for another product of the same MAH(*)	IB

		Procedure type
C.II.8 Change in the frequency and/or date of submission of periodic safety update reports (PSUR)		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

D. Changes to PMF/VAMF	Procedure type
Other variation	1.1.1.1.78 ☐*IA* ☐*IB* ☐*II*

	Procedure type	
D.1 Change in the name and/or address of the VAMF certificate holder		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type	
D.2 Change in the name and/or address of the PMF certificate holder		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type	
D.3 Change or transfer of the current PMF certificate holder to a new PMF certificate holder -i.e. different legal entity-		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type	
D.4 Change in the name and/or address of a blood establishment including blood/plasma collection centres		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type
D.5 Replacement or addition of a blood/plasma collection centre within a blood establishment already included in the PMF	IB

	Procedure type	
D.6 Deletion or change of status (operational/non-operational) of establishment(s)/centre(s) used for blood/plasma collection or in the testing of donations and plasma pools		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type

D.7 Addition of a new blood establishment for the collection of blood/plasma not included in the PMF	II

	Procedure type
D.8 Replacement or addition of a blood centre for testing of donations and/or plasma pools within an establishment already included in the PMF	IB

	Procedure type
D.9 Addition of a new blood establishment for testing of donations and/or plasma pool not included in the PMF	II

	Procedure type
D.10 Replacement or addition of a new blood establishment or centre(s) in which storage of plasma is carried out	IB

		Procedure type
D.11 Deletion of a blood establishment or centre(s) in which storage of plasma is carried out		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type
D.12 Replacement or addition of an organisation involved in the transport of plasma.	IB

		Procedure type
D.13 Deletion of an organisation involved in the transport of plasma		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

		Procedure type
D.14 Addition of a CE-marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

D.15 Addition of a non-CE marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit	Procedure type	
The new test kit has not previously been approved in the PMF for any blood centre for testing of donations	II	
The new test kit has been approved in the PMF for other blood centre(s) for testing of donations		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type
D.16 Change of kit/method used to test pools (antibody or antigen or NAT test).	II

	Procedure type	
D.17 Introduction or extension of inventory hold procedure.		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type
D.18 Removal of inventory hold period or reduction in its length.	IB

D.19 Replacement or addition of blood containers (e.g. bags, bottles)	Procedure type	
The new blood containers are CE-marked		☐IB¤
The new blood containers are not CE-marked	II	

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

D.20 Change in storage / transport	Procedure type	
storage and/or transport conditions		☐IB¤
maximum storage time for the plasma		☐IB¤

¤ If one of the conditions is not met and the change is not specifically listed as Type II.

	Procedure type
D.21 Introduction of test for viral markers when this introduction will have significant impact on the viral risk assessment.	II

	Procedure type
D.22 Change in the plasma pool preparation (e.g. manufacturing method, pool size, storage of plasma pool samples)	IB

	Procedure type
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).	II

Annex II - Extension of marketing authorization

1. Changes to the active substance:

1.1. replacement of the active chemical substance by another salt / ester complex / derivative, with the same therapeutic effect, where the safety/efficiency characteristics do not change significantly;

1.2. replacement by another isomer, a different mixture of isomers, or by a mixture of isolated isomers (e.g. racemate from a single enantiomer), where the safety/efficacy characteristics do not change significantly;

1.3. replacement of the active biological substance with a small change of the molecular structure where the safety/efficacy characteristics do not change significantly, except for:

1.3.1. Changes in the active substance of pandemic or pre-pandemic seasonal human influenza vaccines;

1.4. modification of the vector used to produce the antigen or source material, including new master cell bank from another source, where the safety/efficacy characteristics do not change significantly;

1.5. new binding or coupling mechanism for radiopharmaceuticals where safety/efficacy characteristics do not change significantly;

1.6. changing the extraction solvent or the ratio of herbal drug to herbal preparation where the safety/efficacy characteristics do not change significantly.

2. Changes in strength (dose), pharmaceutical form and method of administration:

2.1. change of bioavailability;

2.2. change of pharmacokinetic properties e.g. change in release ratio;

2.3. change or addition of new dosage/potency;

2.4. change or addition of a new pharmaceutical form;

2.5. change or addition of a new form of administration. For parenteral administration, it is necessary to differentiate between intra-arterial, intravenous, intramuscular or subcutaneous routes. For administration through the air, respiratory system, oral and ocular routes (nebulization) used for vaccines are considered equivalent routes of administration.

Annex III - Classification of Variations

1. The following variations shall be classified as type I minor variations:

1.1. variations of purely administrative nature relating to the identity and contact details of:

1.1.1. Marketing authorization holders;

1.1.2. Manufacturers or suppliers of the raw material, reagent, intermediate product, active substance used in the manufacturing process or the finished product.

1.2. variations related to the deletion of any manufacturing site, including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place;

1.3. variations related to minor changes to an approved physico-chemical test procedure, where the updated procedure is demonstrated to be at least equivalent to the former test procedure, appropriate validation studies have been performed and the results show that the updated test procedure is at least equivalent to the former;

1.4. variations related to changes made to the specifications of the active substance or of an excipient in order to comply with an update of the relevant monograph of the European Pharmacopoeia or of the national pharmacopoeia of a Member State, where the change is made exclusively to comply with the pharmacopoeia and the specifications for product specific properties are unchanged;

1.5. variations related to changes in the packaging material not in contact with the finished product, which do not affect the delivery, use, safety or stability of the medicinal product;

1.6. variations related to the tightening of specification limits, where the change is not a consequence of any commitment from previous assessment to review specification limits and does not result from unexpected events arising during manufacture.

2. The following variations shall be classified as major variations of type II:

2.1. variations related to the addition of a new therapeutic indication or to the modification of an existing one;

2.2. variations related to significant modifications of the summary of product characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance findings;

2.3. variations related to changes outside the range of approved specifications, limits or acceptance criteria;

2.4. variations related to substantial changes to the manufacturing process, formulation, specifications or impurity profile of the active substance or finished medicinal product which may have a significant impact on the quality, safety or efficacy of the medicinal product;

2.5. variations related to modifications in the manufacturing process or sites of the active substance for a biological medicinal product;

2.6. variations related to the introduction of a new design space or the extension of an approved one, where the design space has been developed in accordance with the relevant European and international scientific guidelines;

2.7. variations related to changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza;

Annex IV - Cases for grouping variations referred to in Article 7 paragraph 1.2

1. One of the variations in the group is an extension of the marketing authorisation.
2. One of the variations in the group is a major variation of type II; all other variations in the group are variations which are consequential to this major variation of type II.

3. One of the variations in the group is a minor variation of type IB; all other variations in the group are minor variations which are consequential to this minor variation of type IB.
4. All variations in the group relate solely to changes of administrative nature to the summary of product characteristics, labelling and package leaflet or insert.
5. All variations in the group are changes to an Active Substance Master File, Vaccine Antigen Master File or Plasma Master File

6. All variations in the group relate to a project intended to improve the manufacturing process and the quality of the medicinal product concerned or its active substance(s).
7. All variations in the group are changes affecting the quality of a human pandemic influenza vaccine.
8. All variations in the group relate to the implementation of a given class labelling.
9. All variations in the group are consequential to the assessment of a given periodic safety update report.
10. All variations in the group are consequential to a given post-authorisation study conducted under the supervision of the Marketing Authorization Holder.

Annex V - Elements to be submitted

1. A list of all the marketing authorisations affected by the notification or application.
2. A description of all the variations submitted, including:

   2.1 in the case of minor variations of type I, the date of implementation for each variation described;
   2.2 in the case of minor variations of type I which do not require immediate notification, a description of all minor variations of type I made in the last 12 months to the terms of the concerned marketing authorisation(s) and which have not been already notified.
3. All necessary documents as listed in the guidelines and documentation in article 6, 13 and 14.
4. Where a variation leads to or is the consequence of other variations to the terms of the same marketing authorisation, a description of the relation between these variations is required.

ANNEX VI

ROADMAP OF DOCUMENTATION BY TYPE OF PROCEDURES FOR APPLICATION OF VARIATIONS OF MEDICINAL PRODUCTS

A. ADMINISTRATIVE CHANGES

A.1 Change in the name and/or address of the marketing authorization holder	Conditions that are met	Documentation to be supplied	Type of procedure
	1	1, 2	IA_{IN}

Conditions

1. The marketing authorization holder must remain the same legal entity.

1.1.1.1.2 Documentation

1. An official document from a relevant official body (e.g. Chamber of Commerce) mentioning the new name or new address.

2. Revised product information.

A.2 Change in the (invented) name of the medicinal product	Conditions that are met	Documentation to be supplied	Type of procedure
a) for authorized centralized products	1	1, 2	IA_{IN}
b) for national authorized products		2	IB

1.1.1.1.3 Conditions

1. The check by EMA on the acceptability of the new name has been finalized and was positive.

1.1.1.1.4 Documentation

1. Copy of acceptance letter from EMA of new (invented) name.

2. Revised product information.

A.3 Changing the name of the active substance or an excipient	Conditions that are met	Documentation to be supplied	Type of procedure
	1, 2	1, 2	IA_{IN}

1.1.1.1.5 Conditions

1. The active substance/excipient must remain the same.

2. For veterinary medicinal products for food-producing species, the new name has been published in Regulation (EC) No. 470/2009 of the European Parliament and of the Council of May 6, 2009, which establishes Community procedures for determining the limits of residues of pharmacologically active substances in foods of animal origin, repealing Council Regulation (EEC) No. 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No. 726/2004 of the European Parliament and of the Council before the implementation of this change.

1.1.1.1.6 Documentation

1. Proof of acceptance by WHO or copy of INN list. If applicable, evidence that the change is in accordance with the Ph. Eur. For the herbal medicinal product, the statement that the name is in accordance with the Note on the Guidelines for the Quality of Herbal Medicinal Products and the guideline for the statement of herbal substances and herbal preparations in traditional herbal medicinal products.

2. Revised product information

A.4 Change in the name and/or address of: a manufacturer (including relevant quality control locations); or an ASMF holder; or the supplier of the active substance, starting material, reagent or intermediate used in the production of the active substance (where specified in the technical file) where there is no Ph. Eur. The Certificate of Eligibility is part of the approved file; or a manufacturer of a new excipient (where specified in the technical file)	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
	1	**1, 2, 3**	**IA**

1.1.1.1.7 Conditions

1. The place of manufacture and all manufacturing operations must remain the same.

1.1.1.1.8 Documentation

1. An official document from a relevant official body (e.g. Chamber of Commerce) mentioning the new name and/or new address.
2. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.
3. In case of change of the name of the title holder of the main document of the active substance, the update of the "letter of access".

A.5 Change in the name and / or address of a manufacturer / importer of the finished product (including batch release or quality control)	**Conditions that are met**	**Documentation to be supplied**	**Type of 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 the release of the series	**1**	**1, 2**	**IA**

1.1.1.1.9 Conditions

1. The place of production subject to change of name and / or address and all production operations must remain the same.

1.1.1.1.10 Documentation

1. Copy of the modified production authorization, if possible; or an official document from a relevant official body (e.g. Chamber of Commerce, or if not possible, from a Regulatory Agency) mentioning the new name and/or address.
2. If applicable, amendment of the relevant sections of the file (submitted in EU-CTD format or NTA 6B format of veterinary products volume, as appropriate), including revised product information as appropriate.

A.6. Change in ATC code / ATCvet Code	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
	1	**1, 2**	**IA**

1.1.1.1.11 Conditions

1. Change after the issuance or amendment of the ATC Code by WHO/ ATCvet Code.

1.1.1.1.12 Documentation

1. Proof of acceptance (from WHO) or copy of ATC code list (Vet).
2. Revised product information

A.7 Deleting of manufacturing country for an active substance, intermediate or finished product, packaging country, manufacturer responsible for batch release, place where batch control is performed or supplier of a starting material, reagent or excipient (when mentioned in folder)(*)	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
	1, 2	**1, 2**	**IA**

1.1.1.1.13 Conditions

1. At least one place/producer, as previously authorized, must remain performing the same function as the one(s) relating to the deletion. Where applicable, at least one manufacturer responsible for batch release who is able to validate product testing for batch release purposes within the EU/EEA remains in the EU/EEA.

2. Deleting must not be due to critical manufacturing defects.

1.1.1.1.14 Documentation

1. The variation application form must clearly describe the "present" and "proposed" manufacturers as listed in section 2.5 of the application form for marketing authorizations.

2. Amendment of relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.

(*) Note: where notification has been given by the authorities for the purpose of carrying out an inspection, the erasure of the relevant area will be notified immediately.

A.8 Changes in the date of the audit to verify the GMP compliance of the manufacturer of the active substance(*)	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
			IA

1.1.1.1.15 Documentation

1. Written certification from the manufacturer of the finished product certifying the compliance of the manufacturer of the active substance with the principles and guidelines of good manufacturing practices.

(*) Note: this change does not apply when the information is otherwise transmitted to the authorities (e.g. through a so-called 'QP statement').

B. CHANGES IN QUALITY

B.I ACTIVE SUBSTANCE

B.I.a) *Production*

B.I.a.1 Change in the manufacturer of a starting material / reagent / intermediates used in the production process of the active substance or change in the manufacturer (including the relevant quality control places) of the active substance, where there is no Ph. Eur. The Certificate of Eligibility is part of the approved file	**Conditions that are met**	**Documentation to be supplied**	**Type of 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**	**IA_{IN}**
b) Presentation of an active substance manufacturer supported by an ASMF			**II**
c) The proposed manufacturer uses an essential route of synthesis or manufacturing conditions, which may have the potential to alter important quality characteristics of the active substance, such as qualitative and/or quantitative incompatibility profiles requiring qualifications or physical - chemicals properties that affect bioavailability			**II**
d) New manufacturer of material for whom a viral safety and/or BSE risk assessment is required			**II**

e) The change is related to a biologically active substance or to a starting material / reagent / intermediates used in the production of a biological / immunological product			**II**
f) Changes in quality control testing arrangements for the replacement of the active substance or the addition of a place where the control / testing of the series is carried out	**2, 4**	**1, 5**	**IA**
g) Introducing a new active substance manufacturer that is not supported by an ASMF and requires significant updating of the relevant active substance section of the file			**II**
h) Adding an alternative sterilization place for the active substance using a Ph.Eur. method		**1, 2, 4, 5, 8**	**IB**
i) Introducing a new micronization place	**2, 5**	**1, 4, 5, 6**	**IA**
j) Changes in quality control testing arrangements for a biologically active substance: replacement or adding a place where control / batch testing is performed including a biological / immunological / immunochemical method			**II**
k) New storage location of Master Cell Bank and/or working Cell Banks		**1, 5**	**IB**

1.1.1.1.16 Conditions

1. For starting materials and reagents the specifications (including process controls, methods of analysis of all materials) are identical to those already approved. For intermediaries and active substances the specifications (including process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed synthesis route are identical to those approved.

2. The active substance is not a biological / immunological or sterile substance.

3. When materials of human or animal origin are used in the process, the manufacturer does not use any new suppliers for whom is required evaluation of viral safety or compliance with the *current Guidance Note on Minimizing the Risk of Transmission of Animal Spongiform Encephalopathy Agents through Human and Veterinary Medicinal Products.*

4. The transfer of the method from the old place to the new place has been completed successfully.

5. The specification of the particle size of the active substance and the corresponding analytical method remain the same.

1.1.1.1.17 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

2. A statement by the marketing authorization holder or SMSA holder, where applicable, that the synthetic route (or in the case of herbal medicinal products, where appropriate the method of preparation, the geographical source, the production of the herbal medicinal product and the route of production) procedures and specifications of the active substance and of the starting material / reagent / intermediates in the production process of the active substance (if applicable) are the same as those approved.

3. Or a TSE Ph. Eur. Certificate of Conformity for each new source of material or, where possible, documentary evidence that the specific source of TSE risk material has been pre-assessed by the competent authority and shown to be in accordance with the *current Risk Minimization Guidance Note of Animal Distribution of Spongiform Encephalopathy Agents through Human and Veterinary Medicinal Products*. The information should include: Manufacturer's name, species and tissues from which the material is derived, country of origin of the source animal, its use and prior acceptance. For the Centralized Procedure, this information must be included in an updated TSE table A (and B, if relevant).

4. Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the active substance from current and proposed manufacturers/places.

5. The change application form should clearly describe the "present" and "proposed" manufacturers as they are noted in part 2.5 of the marketing authorization application form.

6. A statement from the qualified person (QP) of each of the manufacturing authorization holders listed in the application where the active substance is used as starting material and a statement from the qualified person (QP) of each of the manufacturing authorization holders In the application as responsible for release from collection. These statements must state that the manufacturers of the active substances mentioned in the application act in accordance with detailed guidelines for good manufacturing practices for starting materials. A single statement may be acceptable in certain circumstances - see note under amendment no. B.II.b.1.

7. Where relevant, the commitment of the manufacturer of the active substance to inform the MA holder of any changes in the manufacturing process, specifications and testing procedures of the active substance.

8. Evidence that the proposed country is appropriately authorized for the pharmaceutical form or product or manufacturing operation in question, e.g.:

   For a manufacturing country within the EU/EEA: a copy of the current manufacturing authorization. A reference to the EudraPMP database will suffice.

   For a production country outside the EU/EEA, where there is an operational GMP mutual recognition agreement (MRE) between the relevant country and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority.

   For a production country outside the EU/EEA, where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the EU/EEA Member States. A reference to the EudraPMP database will suffice.

B.I.a.2 Changes in the production process of the active substance	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Small changes in the production process of the active substance	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 3**	**IA**
b) Substantial change in the production process of the active substance that may have a significant impact on the quality, safety or efficacy of the medicinal product			**II**
c) The change concerns a biological / immunological substance or the use of a different chemically derived substance in the production of a biological / immunological substance, which may have a significant impact on the quality, safety and efficacy of the medicinal product and is not bound to a protocol			**II**

d) The change concerns a herbal medicinal product and there is a change in any of the following: geographical source, route of production or production			**II**
e) Minor change in the limited part of a master file of active substances		**1, 2, 3, 4**	**IB**

1.1.1.1.18 Conditions

1. No adverse change in qualitative and quantitative impurity profile or physico-chemical properties.

2. The synthetic route remains the same, i.e. the mediators 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, the production of the herbal substance and the route of production remain the same.

3. The specifications of the active or intermediate substance are unchanged.

4. The change is fully described in the open part ('applicant') of a master dossier of the active substance, if applicable.

5. The active substance is not a biological / immunological substance.

6. The change does not refer to the geographical source, production route or production of a herbal medicinal product.

7. The change does not refer to the restricted part of an Active Substances Master File.

1.1.1.1.19 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate) and of the approved main active substance dossier (where applicable), including a direct comparison of the current process and new process.

2. Collection analysis data (in comparative tabular format) of at least two batches (minimum pilot scale) produced according to the currently approved and proposed process.

3. Copy of the approved specifications of the active substance.

4. A statement from the Marketing Authorization Holder or SMSA Holder, where applicable, that there is no change in the qualitative and quantitative incompatibility profile or in the physico-chemical properties, that the synthetic route remains the same and that the specifications of the active substance or brokers are unchanged.

Note: for BIa2.b), for chemical active substances, this refers to substantial changes in the synthetic route or production conditions which may have the potential to change important quality characteristics of the active substance, such as the qualitative and/or quantitative profile of impurity that requires qualification, or physico-chemical properties that affect bioavailability.

B.I.a.3 Variation in batch size (including batch size ranges) of the active substance or intermediate used in the active substance manufacturing process	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Up to 10-times increase compared to the originally approved batch size	**1, 2, 3, 4, 6, 7, 8**	**1, 2, 5**	**IA**
b) Reduction up to 10-times	**1, 2, 3, 4, 5**	**1, 2, 5**	**IA**
c) The change requires the evaluation of the comparability of the biological / immunological active substance			**II**

d) More than 10-times increase compared to the originally approved batch size		**1, 2, 3, 4**	**IB**
e) Rate for a biologically/immunologically active substance increases/decreases without process change (e.g. line doubling)		**1, 2, 3, 4**	**IB**

1.1.1.1.20 Conditions

1. Any changes in the production methods are only those necessary from the increase or decrease, e.g. the use of different devices.

2. Test results of at least two batches to specifications shall be available for the proposed batch size.

3. The product in question is not a biological / immunological medicinal product.

4. The change does not adversely affect the reproducibility of the process.

5. The change must not be the result of unexpected events occurring during production or due to stability concerns.

6. The specifications of the active / intermediate substance remain the same.

7. The active substance is not sterile.

8. The batch size is within the range of ten times the batch size envisaged when the marketing authorization was granted or after a subsequent change was not agreed as a type IA variant.

1.1.1.1.21 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

2. Batch numbers of batches tested having the proposed batch size.

3. Batch analysis data (in a comparative tabular format) on a minimum of one production batch of the active substance or intermediate as appropriate, produced in both approved and proposed sizes. Collection data on the other two production batches should be made available upon request and reported by the marketing authorization holder if external specifications (with proposed action).

4. Copy of approved active substance (and intermediate, if applicable) specifications.

5 A statement from the marketing authorization holder or ASMF holder as appropriate that the changes in production methods are only those required by scaling up or downsizing, e.g. The use of different equipment, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during production or due to stability concerns and that the specifications of the active substance / intermediates remain the same.

B.I.a.4 Change in in-process tests or limits applied during production of the active substance	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Tightening the borders in the process	**1, 2, 3, 4**	**1, 2**	**IA**
b) Adding a piece of evidence and new limits to the process	**1, 2, 5, 6**	**1, 2, 3, 4, 6**	**IA**
c) Deleting a non-relevant piece of evidence in the process	**1, 2, 7**	**1, 2, 5**	**IA**
d) Extending the testing limits adopted in the process, which may have a significant effect on the overall quality of the active substance			**II**
e) Deleting of a process in the process, which may have a significant effect on the overall quality of the active substance			**II**
f) Adding or replacing an in-process test as a result of a safety or quality problem		**1, 2, 3, 4, 6**	**IB**

1.1.1.1.22 Conditions

The change is not a consequence of any commitment from previous evaluations to review the specification limits (e.g. made during the procedure for the application for marketing authorization or for a type II variation procedure).

1. The change does not come from unexpected events that arise during production, e.g. unqualified young dirt; change in total impurity limits.

2. Any changes must be within the currently approved limits.

3. The test procedure remains the same, or the changes in the test procedure are minor.

4. Any new test method is not about a new non-standard technique or a standard technique used in a new way.

5. The new test method is not a biological / immunological / immunochemical method or a method that uses a biological reagent for an active biological substance (does not include standard pharmacopoeial microbiological methods).

6. The specification parameter does not relate to a critical parameter for example any of the following: analysis, impurities (unless a particular solvent is definitely not used in the production of the active substance), any critical physical characteristic, e.g. Particle size, bulk or density struck, identity test, water, any requirement to change test frequency.

1.1.1.1.23 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

2. Comparison table of current and proposed tests in progress.

3. Details of any new non-pharmacopoeial analytical methods and validation data, where appropriate.

4. Batch analysis data in two production batches (3 production batches for biologics, unless otherwise justified) of the active substance for all specification parameters.

5. Justification / risk assessment by the Marketing Authorization Holder or the ASMF Holder, as applicable, that the in-process tests are not relevant or that the in-process tests are out of date.

6. Justification by MAH Holder or ASMF as appropriate for new test in process and limits.

B.Ia.5 Changes in the active substance of the seasonal, pre-pandemic or pandemic human influenza vaccine	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Substitution of the type in a seasonal, pre-pandemic or pandemic vaccine against human influenza			**II**

B.I.b) *Control of the active substance*

B.I.b.1 Change in the specification parameters and / or limits of an active substance, starting material / intermediate / reagent used in the production process of the active substance	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**

a) Tightening of specification limits for medicinal products subject to the Official Authorization of the Control Authority	**1, 2, 3, 4**	**1, 2**	**IA_{IN}**
b) Tightening the specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
c) Adding a new specification parameter to the specification with the corresponding test method	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 7**	**IA**
d) Deleting an unimportant specification parameter (e.g. deleting an obsolete parameter)	**1, 2, 8**	**1, 2, 6**	**IA**
e) Deleting of a specification parameter that may have a significant effect on the overall quality of the active substance and/or the finished product			**II**
f) Variation outside the limits of the approved specifications depends on the active substance			**II**

g) Extending the specified limits approved for starting materials / intermediates, which may have a significant effect on the overall quality of the active substance and / or the finished product			**II**
h) Addition or replacement (except for biological or immunological substance) of a specification parameter with the corresponding test method as a result of a safety or quality problem		**1, 2, 3, 4, 5, 7**	**IB**
i) When there is no monograph in the European Pharmacopoeia or in the national pharmacopoeia of a Member State for the active substance, a change in the specification from home to a Pharmacopoeia or to a Pharmacopoeia of a third country		**1, 2, 3, 4, 5, 7**	**IB**

1.1.1.1.24 Conditions

1. The change is not a consequence of any commitment from previous evaluations to review the specification limits (e.g. made during the procedure for the application for marketing authorization or for a type II variation procedure).

2. The change does not come from unexpected events that arise during production, e.g. Unqualified new impurity; Change in total impurity limits.

3. Any changes must be within the currently approved limits.

4. The test procedure remains the same, or the changes in the test procedure are minor.

5. Any new test method does not involve a new non-standard technique or a standard technique used in a new way.

6. The test method is not a biological / immunological / immunochemical method or a method that uses a biological reagent for an active biological substance (does not include standard microbiological pharmacopoeia methods).

7. For each material, the difference is not about genotoxic impurity. If it includes the final active substance, in addition to waste solvents that must comply with ICH / VICH limits, any new impurity control must comply with Ph. Eur. Or the National Pharmacopoeia of a Member State.

8. The specification parameter does not relate to a critical parameter, for example any of the following: analysis, impurities (unless a specific solvent is definitely not used in the production of the active substance), any critical physical characteristic, e.g. Particle size, bulk or intercepted density, identity testing, water, any pass testing requirements.

1.1.1.1.25 Documentation

1. Amendment of the relevant sections of the dossier (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

2. Comparison table of current and proposed specifications.

3. Details of any new analytical methods and validation data, where appropriate.

4. Batch analysis data in two production batches (3 production batches for biologics, unless otherwise justified) of the relevant substance for all specification parameters.

5. Where appropriate, comparative distribution profile data for the finished product in at least one pilot batch containing the active substance conforming to current and proposed specifications. For herbal medicinal products, comparative dissolution data may be acceptable.

6. Justification / risk assessment by the Marketing Authorization Holder or ASMF Holder, as applicable, that the parameter in the process is not relevant or that the parameter in the process is outdated.

7. Justification by MAH Holder or ASMF as appropriate for new specification parameters and limits.

B.I.b.2 Change in the testing process for the active substance or the starting material / reagent / intermediate used in the process of processing the active substance	Conditions that are met	Documentation to be supplied	Type of procedure
a) Minor changes to an approved test procedure	1, 2, 3, 4	1, 2	IA
b) Deleting a test procedure for the active substance or a starting material / reagent / intermediate, if an alternative test procedure is already authorized.	7	1	IA
c) Other changes to a test procedure (including substitution or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance	1, 2, 3, 5, 6	1, 2	IA
d) Substantial change or substitution of a biological / immunological / immunochemical test method or a method that uses a biological reagent for an active biological substance			II
e) Other changes in a test process (including substitution or addition) for the active substance or a starting/intermediate material		1, 2	IB

1.1.1.1.26 Conditions

1. Adequate validation studies have been performed in accordance with relevant guidelines and demonstrate that the updated test procedure is at least equivalent to the previous test procedure.

2. There were no changes in total impurity limits; No new unqualified impurities are detected.

3. The method of analysis must remain the same (e.g. a change in column length or temperature, but not a different column or method).

4. The test method is not a biological / immunological / immunochemical method, or a method that uses a biological reagent for a biologically active substance (does not include standard microbiological pharmacopoeial methods).

5. Any new test method does not involve a new non-standard technique or a standard technique used in a new way.

6. The active substance is not biological / immunological.

7 An alternative test procedure is already authorized for the specification parameters and this procedure has not been added through the IA / IA (IN) notification.

1.1.1.1.27 Documentation

1. Amendment of the relevant sections of the dossier (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate, including a description of the analytical methodology, a summary of validation data, revised impurity specifications (if applicable).

2. The results of the validation comparison, or if the results of the justified comparative analysis show that the actual test and the proposal are equivalent. This requirement is not applicable in case of adding a new test procedure.

B.I.c) *Container closure system*

B.I.c.1 Change in the immediate packaging of the active substance	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Qualitative and/or quantitative composition	**1, 2, 3**	**1, 2, 3, 4, 6**	**IA**

b) Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances			**II**
c) Liquid active substances (non-sterile)		**1, 2, 3, 5, 6**	**IB**

1.1.1.1.28 Conditions

1. The proposed packaging material must be at least equivalent to the approved material in terms of its respective properties.

2 Relevant stability studies have been initiated according to ICH/VICH parameters Relevant stability conditions and parameters have been evaluated in at least two pilot batches or industrial scale and at least 3 months of stable stability data are available to the applicant at the time of application. However, if the proposed packaging is more resistant than the existing packaging, 3-month stability data should not yet be available. These studies must be finalized and the data will be provided immediately to the competent authorities if the external specifications or potential specifications outside at the end of the acceptance / repetition period (with proposed action).

3 Sterile, liquid and biological / immunological active substances are excluded.

1.1.1.1.29 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

2. Appropriate data for the new packaging (e.g. comparative permeability data, e.g. for O2, CO2 humidity), including confirmation that the material complies with relevant pharmacopoeial requirements or Union legislation on materials plastic and objects in contact with food.

3. Where appropriate, evidence should be provided that there is no interaction between the contents and the packaging material (e.g. no migration of components of the proposed material into the contents and no loss of product components into the packaging), including confirmation that the Material is in accordance with the relevant requirements of the pharmacopoeia or Union legislation on plastic materials and objects in contact with food.

4. A statement from the marketing authorization holder or ASMF holder, as applicable, that the required stability studies have been initiated under ICH/VICH conditions (marking the relevant batch numbers) and that, as appropriate, Available to the applicant at the time of implementation and that the available data did not show any problems. It must also be ensured that the studies will be finalized and that the data will be immediately provided to the competent authorities if the external specifications or possible specifications outside at the end of the approved period (with proposed action).

5. The results of stability studies that have been carried out according to ICH/VICH conditions, on the relevant stability parameters, in at least two pilot or industrial groups, covering a minimum period of 3 months and an assurance has been given that these studies will be finalized and that the data will be immediately provided to the competent authorities if out-of-spec or potential out-of-spec at the end of the approved requalification period (with proposed action).

6. Comparison of current and proposed immediate packaging specifications, if applicable.

B.I.c.2 Change in the specification parameters and / or limits of immediate packaging of the active substance	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Tightening the specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Adding a new specification parameter to the specification with the corresponding test method	**1, 2, 5**	**1, 2, 3, 4, 6**	**IA**
c) Deleting an unimportant specification parameter (e.g. deleting an obsolete parameter)	**1, 2**	**1, 2, 5**	**IA**
d) Adding or replacing a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4, 6**	**IB**

1.1.1.1.30 Conditions

The change is not a consequence of any commitment from previous assessments to review the specification limits (e.g. made during the marketing authorization application procedure or type II variation procedure) unless it has been previously assessed and agreed as part of a follow-up measure process.

1. The change does not result from unexpected events that arise during the production of the packaging material or during the storage of the active substance.

2. Any changes must be within the currently approved limits.

3. The test procedure remains the same, or the changes in the test procedure are minor.

4. Any new test method is not about a new non-standard technique or a standard technique used in a new way.

1.1.1.1.31 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

2. Comparison table of current and proposed specifications.

3. Details of any new analytical methods and validation data, where appropriate.

4. Series analysis data in two sets of immediate packaging for all specification parameters.

5 Justification / risk assessment by the Marketing Authorization Holder or the ASMF Holder, as the case may be, that the in-process parameter is not relevant or that the in-process parameter is outdated.

6. Justification by the marketing authorization holder or ASMF Holder, as the case may be, of the new specification parameter and limits.

B.I.c.3 Change in test procedure for immediate packaging of active substance	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Minor changes to an approved test procedure	**1, 2, 3,**	**1, 2**	**IA**

b) Other changes to a test process (including replacement or addition)	**1, 3, 4**	**1, 2**	**IA**
c) Deleting a test procedure if an alternative test procedure is already authorized	**5**	**1**	**IA**

1.1.1.1.32 Conditions

1. Adequate validation studies have been performed in accordance with relevant guidelines and demonstrate that the updated test procedure is at least equivalent to the previous test procedure.

2. The method of analysis must remain the same (e.g. a change in column length or temperature, but not a different column or method).

3. Any new test method does not involve a new non-standard technique or a standard technique used in a new way.

4. The active substance / finished product is not biological / immunological.

5. There is still a registered test procedure for the specification parameters and this procedure has not been added through an IA / IA (IN) notification.

1.1.1.1.33 Documentation

1. Amendment of relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate, including a description of the analytical methodology, a summary of the validation data.

2. The results of the validation comparison or if the results of the justified comparative analysis show that the actual test and the proposal are equivalent. This requirement is not applicable in case of adding a new test procedure.

B.I.d) *Stability*

B.I.d.1 Change in the rehabilitation period / period of storage or storage Conditions of the active substance where there is no Ph. Eur. The certificate of eligibility covering the test period is part of the approved file	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Retest period / storage period			
1. Reduction	**1**	**1, 2, 3**	**IA**
2. Extension of testing period based on extra adding of stability data not in accordance with ICH / VICH guidelines(*)			**II**
3. Extending the storage period of a biological / immunological active substance that does not comply with an approved stability protocol			**II**
4. Extension or introduction of retry period / retention period supported by real-time data		**1, 2, 3**	**IB**
b) Storage conditions			
1. Change to more restrictive storage conditions of the active substance	**1**	**1, 2, 3**	**IA**
2. Changing in the storage conditions of biologically active / immunological substances, when stability studies have not been performed in accordance with a currently approved stability protocol			**II**
3. Change in the storage conditions of the active substance		**1, 2, 3**	**IB**
c) Change to an approved stability protocol	**1, 2**	**1, 4**	**IA**

1.1.1.1.34 Conditions

1. The change must not be the result of unexpected events occurring during production or due to stability concerns.

2. The changes are not related to the expansion of the acceptance criteria in the tested parameters, the removal of the stability indicating parameters or the reduction of the frequency of testing.

1.1.1.1.35 Documentation

1. Amendment of relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as applicable). This should contain the results of appropriate real-time stability studies,

carried out in accordance with the relevant stability guidelines for at least two (three for biological medicinal products) pilot or production-scale batches of the active substance in the authorized packaging material and covering the required duration of the test period or storage conditions required.

2. Confirmation that stability studies have been performed in the currently approved protocol. The studies must show that the relevant tuned specifications are still met.

3. Copy of the approved specifications of the active substance.

4. Justification for proposed changes.

(*) *Note*: The retest period is not applicable for the biological / immunological active substance.

B.I.e) *Design spaces and post-approval change management protocols*

B.I.e.1 Introduction of a new design space or extension of the approved design space for the active substance, in relation to:	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) A unit operation in the production process of the active substance including the resulting process controls and/or testing procedures		**1, 2, 3**	**II**
b) Test procedures for starting materials / reagents / intermediates and/or active substance		**1, 2, 3**	**II**

1.1.1.1.36 Documentation

1. The design space has been developed in accordance with relevant European and international scientific guidelines. The results of product, process and analytical development studies should be studied (e.g. the interaction of the various parameters that shape the design space, including risk assessment and multivariate studies, as appropriate) indicating where it is important that a Systematic mechanistic understanding of material attributes and process parameters Critical quality attributes of the active substance are achieved.

2. Description of the Design space in tabular format, including variables (material attributes and process parameters, as appropriate) and their proposed ranges.

3. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

B.I.e.2 Introduction of a post-approval change management protocol related to the active substance	Conditions that are met	Documentation to be supplied	Type of procedure
		1, 2, 3	**II**

1.1.1.1.37 Documentation

1. Detailed description of the proposed change.
2. Change the management protocol regarding the active substance1.
3. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

B.I.e.3 Deleting an approved change management protocol related to the active substance	Conditions that are met	Documentation to be supplied	Type of procedure
	1	**1, 2**	**IA_{IN}**

1.1.1.1.38 Conditions

1. Deleting the approved change management protocol related to the active substance is not the result of unexpected events or specified results during the implementation of the changes described in the protocol and have no effect on the information already approved in the file.

1.1.1.1.39 Documentation

1. Reason for proposed deletion.
2. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

B.I.e.4 Changes to an approved change management protocol	Conditions that are met	Documentation to be supplied	Type of 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

1.1.1.1.40 Documentation

1. Stating that any changes must be within the currently approved limits. In addition, the statement that a comparability assessment is not required for biological / immunological medicinal products.

B.I.e.5 Implementation of changes foreseen in an approved change management protocol	Conditions that are met	Documentation to be supplied	Type of procedure
a) Implementation of the change does not require further supporting data	1	1, 2, 4	IA_{IN}
b) Implementation of the change requires further supporting data		1, 2, 3, 4	IB
c) Implementation of a change for a biological / immunological medicinal product		1, 2, 3, 4, 5	IB

1.1.1.1.41 Conditions

1. The proposed change is made in full compliance with the approved change management protocol.

1.1.1.1.42 Documentation

1. Reference to approved change management protocol.
2. Statement that the change is consistent with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, the statement that a comparability assessment is not required for biological / immunological medicinal products.
3. Results of studies conducted in accordance with the approved change management protocol.
4. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

5. Copy of the approved specifications of the active substance.

B.II. FINISHED PRODUCT

B.II. a) *Description and composition*

B.II.a.1 Changing or adding printing, covers or other markings, including replacing or adding colors used to mark the product.	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Changes in printing, elevation or other notes	**1, 2, 3, 4**	**1, 2**	**IA_{IN}**

b) Changes in marking / breaking lines intended to divide into equal doses		**1, 2, 3**	**IB**

1.1.1.1.43 Conditions

1. Finished product release and end of shelf life specifications have not changed (except appearance).
2. Each color must comply with the relevant pharmaceutical legislation.
3. Score/break lines are not meant to be divided into equal doses.
4. Product markings used to distinguish strengths should not be completely erased.

1.1.1.1.44 Documentation

1. Amendment of relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a detailed drawing or written description of the current and new appearance and including revised information of product as the case may be.
2. Samples of the finished product where applicable (see NTA, Sample Requirements in Member States).

3 Results of appropriate Ph.Eur tests demonstrating equivalence in characteristics / correct dosage.

B.II.a.2 Change in the shape or dimensions of the pharmaceutical form	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Immediate release of tablets, capsules, suppositories and vaginal suppositories	**1, 2, 3, 4**	**1, 4**	**IA_{IN}**
b) Gastro-resistant pharmaceutical form, modified or extended release, and marked tablets, intended to be divided into equal doses		**1, 2, 3, 4, 5**	**IB**
c) Adding a new kit for a radiopharmaceutical preparation with a different filling volume			**II**

1.1.1.1.45 Conditions

1. If appropriate, the distribution profile of the reformulated product is comparable to the old one. For herbal medicinal products, where dissolution testing may not be possible, the dissolution time of the new product compared to the old.

2. Release and end of product shelf life specifications have not changed (except dimensions).

3. The qualitative or quantitative composition and average mass remain unchanged.

4. The change does not involve a marked tablet that is intended to be divided into equal doses.

1.1.1.1.46 Documentation

1. Amendment of relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate, including a detailed drawing of the current and proposed situation, and including revised product information as necessary.

2. Comparative dissolution data on at least one pilot series of current and proposed dimensions (no significant differences regarding comparability, see relevant guidance (Human or Veterinary Bioavailability). For comparative dissolution data of herbal medicinal products can be acceptable.

3. Reason for not submitting a new bioequivalence study according to relevant (human or veterinary) bioavailability guidelines.

4. Samples of the finished product where applicable (see NTA, Sample Requirements in Member States).

5. Results of appropriate Ph.Eur tests demonstrating equivalence in characteristics / correct dosage.

Note: for B.II.a.2.c), applicants are reminded that any change in the 'strength' of the medicinal product requires the submission of an extension application.

B.II.a.3 Changes in the composition (excipients) of the finished product	Conditions that are met	Documentation to be supplied	Type of procedure
a) Changes in the components of the flavoring or coloring system			
1. Addition, deletion or substitution	**1, 2, 3, 4, 5, 6, 7, 9, 11**	**1, 2, 4, 5, 6**	**IA_{IN}**
2. Increase or decrease	**1, 2, 3, 4, 11**	**1, 2, 4**	**IA**
3. Biological veterinary medicinal products for oral use, for which the coloring or flavoring agent is important for uptake by the target animal species			**II**
b) Other excipients			
1. Any minor adjustment of the quantitative composition of the finished product in relation 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 related to a biological / immunological product			**II**
4. Any new excipient involving the use of materials of human or animal origin for which evaluation of virus safety data or TSE risk is required			**II**
5. Change that is supported by a bioequivalence study			**II**
6. Substitution of a single excipient with a comparable excipient with the same functional functions and at a similar level		**1, 3, 4, 5, 6, 7, 8, 9, 10**	**IB**

1.1.1.1.47 Conditions

1. No change in the functional characteristics of the pharmaceutical form, e.g. disintegration time, disintegration profile.

2. Any minor formulation adjustments to maintain the total weight must be made by an excipient that actually makes up a large portion of the finished product formulation.

3. The specification of the finished product is updated only with respect to appearance / smell / taste and, if appropriate, the deletion of identification proof.

4. Stability studies have been initiated according to ICH / VICH conditions (with cumulative number indicators) and relevant stability parameters have been evaluated in at least two pilot batches or on an industrial scale and at least 3 months of stable stability data are available to Applicant (at the time of application for IAs Type

and at the time of notification for IB) Type and that the stability profile is similar to the currently recorded situation. It is ensured that these studies will be finalized and that the data will be immediately provided to the competent authorities if external specifications or external specifications can be at the end of the approved deadline (with proposed action). In addition, where relevant, photostability testing should be performed.

5. Any new proposed ingredient must comply with the relevant directives (e.g. Directive 94/36/EC of the European Parliament and of the Council (1) and Commission Directive 2008/128/EC (2) on colors for use in foods and Council Directive 88/388/EEC (3) for taste).

6. Any new ingredient does not involve the use of materials of human or animal origin, for which evaluation of virus safety data or compliance with the *Current note for guidance on minimizing the risk of transmission of animal encephalopathy agents through human and veterinary medicine products is required.*

7. Where possible, the change does not affect the differentiation between strengths and does not have any negative impact on the taste acceptability of pediatric formulations.

8. The dissolution profile of the new product determined in a minimum of two pilot groups is comparable to the old one (there are no significant differences regarding comparability, see the relevant guidance (Human or Veterinary Guidance on Bioavailability). For herbal medicinal products where dissolution testing may not be possible, the dissolution time of the new product is comparable to the old one.

9. The change is not a result of stability issues and/or should not result in potential security concerns, ie. Differentiation between forces.

10. The product in question is not a biological / immunological medicinal product.

11. For veterinary medicinal products for oral use, the change does not affect uptake by the target animal species.

1.1.1.1.48 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including the method of identification for any new colorants, where appropriate, and including the revised product information as appropriate.

2. A statement that the necessary stability studies have been initiated under the ICH / VICH conditions (with the sign of the relevant series numbers) and that, as necessary, the minimum required stability data were available to the applicant at the time of implementation and that the data available do not show any problems. It must also be ensured that the studies will be finalized and that the data will be immediately provided to the competent authorities if the external specifications or potential specifications outside are at the end of the approved deadline (with proposed action).

3. The results of stability studies carried out under the conditions of ICH / VICH, on the relevant stability parameters, in at least two pilot or industrial groups, covering a minimum period of 3 months and an assurance has been given that these studies will be finalized and that the data will be immediately provided to the competent authorities if the specifications out or potential specifications outside are at the end of the approved deadline (with proposed action).

4. Sample of the new product, where possible (see Notice on Applicants' Requirements for samples in Member States).

5. Or a Ph Eur. Certificate of Conformity for any new animal components susceptible to BSE risk or where possible, documentary evidence that the specific source of BSE risk material has been pre-assessed by the competent authority and shown to be compliant with the scope of the *current Guidance Note Minimizing the risk of transmission of animal spongiform encephalopathies through human and veterinary medicinal products*. For each such material the following information must be included: Manufacturer's name, species and tissues from which the material is derived, country of origin of the source animal and its use.

   For the Centralized Procedure, this information must be included in an updated TSE Table A (and B, if relevant).

6. Data to demonstrate that the new excipient does not interfere with the test methods of the finished product specification, if appropriate.

7 Justification for change / choice of excipients, etc., should be provided by appropriate development pharmacies (including aspects of stability and antimicrobial storage where appropriate).

8. For solid dosage forms, comparative distribution profile data of at least two pilot batches of the finished product in the new and old formulation. For herbal medicinal products, comparative dissolution data may be acceptable.

9. Justification for not submitting a new bioequivalence study under the *current Note on Bioavailability and Bioequivalence Investigation Guidance..*

10. For veterinary herbs intended for use in food-producing animal species, proof that the excipient is classified according to Article 14 (2) (c) of Regulation (EC) No 470/2009 or, if not, justification that the excipient does not have pharmacological activity in the dose at which it is administered to the target animal.

(1) OJ L 237, 10.9.1994, p. 13.

(2) OJ L 6, 10.1.2009, p. 20.

(3) OJ L 184, 15.7.1988, p. 61.

B.II.a.4 Change in layer weight of oral dosage forms or change in capsule weight	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Solid oral pharmaceutical forms	**1, 2, 3, 4**	**1, 2**	**IA**
b) Gastro-resistant, modified or extended pharmaceutical forms, where coating is a critical factor for the release mechanism			**II**

1.1.1.1.49 Conditions

1. The dissolution profile of the new product determined in a minimum of two pilot runs is comparable to the old one. For herbal medicinal products where dissolution testing may not be possible, the dissolution time of the new product is comparable to the old one.

2. Coating is not a critical factor in the release mechanism.

3. The finished product specification has only been updated with respect to weight and dimensions, if applicable.

4. Stability studies in accordance with the relevant guidelines have been initiated with at least two pilot-scale or industrial-scale samples and at least 3 months of stable stability data are available to the applicant at the time of implementation and assurance that these studies will be finalized. The data will be provided immediately to the competent authorities if the external specifications or potential specifications outside are at the end of the approved period (with proposed action).

1.1.1.1.50 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

2. A statement that the necessary stability studies have been initiated under the ICH / VICH conditions (with the sign of the relevant series numbers) and that, as necessary, the minimum required stability data were available to the applicant at the time of implementation and that the data available do not show any problems. It must also be ensured that the studies will be finalized and that the data will be immediately provided to the competent authorities if the external specifications or potential specifications outside are at the end of the approved deadline (with proposed action). In addition, where relevant, photostability testing should be performed.

B.II.a.5 Variation in the concentration of a single dose, the total parenteral product of use, where the amount of active substance per unit dose (ie, strength) remains the same	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
			II

B.II.a.6 Wipe the container of solvent / diluents from the package	Conditions that are met	Documentation to be supplied	Type of procedure
		1, 2	IB

1.1.1.1.51 Documentation

1. Justification for deletion, including a statement regarding alternative means of obtaining the solvent/diluent as required for the safe and effective use of the medicinal product.

2. Revised product information.

B.II.b) *Produce*

B.II.b.1 Substitution or addition of a place of production for part or all of the production process of the finished product	Conditions that are met	Documentation to be supplied	Type of procedure
a) Place of secondary packaging	**1, 2**	**1, 3, 8**	**IA_{IN}**
b) Place of primary packaging	**1, 2, 3, 4, 5**	**1, 2, 3, 4, 8, 9**	**IA_{IN}**
c) Place where any manufacturing operation is performed, except batch release, collection control and secondary packaging, for biological / immunological medicinal products or for pharmaceutical forms produced by complex manufacturing processes			**II**
d) Place which requires an initial or specific inspection of the product			**II**
e) Place where the manufacturing operations are located, except for batch release, batch control, primary and secondary packaging, for non-sterile medicinal products		**1, 2, 3, 4, 5, 6, 7, 8, 9**	**IB**
f) Place where any manufacturing operation is performed, except for batch release, batch control and secondary packaging, for sterile medicinal products (including those produced aseptically) excluding biological / immunological medicinal products		**1, 2, 3, 4, 5, 6, 7, 8**	**IB**

1.1.1.1.52 Conditions

1. Satisfactory inspection in the last 3 years by an inspection service of one of the EU / EEA Member States or of a country where there is a Good Manufacturing Practice (GMP) Knowledge Recognition Agreement between the relevant country and the EU.

2. Appropriately authorized country (to manufacture the pharmaceutical form or product in question).

3. The product in question is not a sterile product.

4. When it is important, e.g. for suspensions and emulsions, the validation scheme is available or the validation of production in the new country has been successfully performed according to the current protocol with at least three batches at production scale.

5. The product in question is not a biological / immunological medicinal product.

1.1.1.1.53 Documentation

1. Evidence that the proposed country is appropriately authorized for the pharmaceutical form or product in question, ie:

   For a manufacturing country within the EU / EEA: a copy of the current manufacturing authorization. A reference to the EudraGMP database will suffice;

For a manufacturing country outside the EU/EEA, where there is an operational mutual recognition agreement (MOA) between the respective country and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority;

For a production country outside the EU/EEA, where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the EU/EEA Member States. A reference to the EudraGMP database will suffice.

2. When relevant, the batch numbers, corresponding batch size and production date of the batches (≥ 3) used in the validation study should be indicated and the validation data or validation protocol (scheme) to be submitted should be shown.

3. The variation application form must clearly describe the "present" and "proposed" product manufacturers listed in section 2.5 of the application form.

4. Copies of approved releases and filing deadline specifications if relevant.

5. Batch analysis data for one production batch and two pilot batches simulating the production process (or two production batches) and comparative data for the last three batches from the previous country; batch data on the next two production batches should be available upon request or if reported if external specifications (with proposed action).

6. For semi-solid and liquid formulations in which the active substance is present in undissolved form, relevant validation data including microscopic imaging of particle size distribution and morphology or any other appropriate imaging technique.

7. i) If the new manufacturing country uses the active substance as a starting material - A statement from the Qualified Person (QP) at the country responsible for the batch release that the active substance is manufactured in accordance with detailed instructions on good manufacturing practices for starting materials approved by the Union.

ii) In addition, if the new manufacturing country is located within the EU/EEA and uses the active substance as starting material - A statement from the Qualified Person (QP) of the new manufacturing country where the active substance used is manufactured in accordance with the guidelines detailed on good manufacturing practices for starting materials approved by the Union.

8. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

9. If the country of production and the country of primary packaging are different, the conditions of transport and bulk storage must be specified and validated.

Notes:

In the event of a change to a new manufacturing place in a country outside the EU/EEA without an operational PMP mutual recognition agreement with the EU, marketing authorization holders are advised to consult the relevant competent authorities before submitting the notification and To provide information about any previous EU / EEA inspections in the last 2-3 years and / or any planned EU / EEA inspections including inspection dates, product category inspected, Supervisory Authority and other relevant information. This will facilitate the arrangement of a PMP inspection by an inspection service of one of the Member States if necessary.

1.1.1.1.54 KP statement regarding active substances

Manufacturing authorization holders are obliged to only use as starting material active substances that have been manufactured in accordance with the GMP so a statement is expected from each manufacturing authorization holder that uses the active substance as starting material. In addition, as the KP responsible for collection certification takes overall responsibility for each batch, a further statement from the KP responsible for collection certification is expected when the place of release of the batch is other than the above.

In many cases only one manufacturing authorization holder is involved and therefore only one statement is required. However, where more than one manufacturing authorization holder is involved and not multiple statements, it may be acceptable to provide a single statement signed by a KP. This will be accepted provided that:

The statement makes it clear that it is signed on behalf of all KPs involved.

The agreements are supported by a technical agreement as described in Chapter 7 of the GMP Guide and the KP providing the statement is the one identified in the agreement as taking specific responsibility for the GMP compliance of the manufacturer(s) of the active substances. Note: these agreements are subject to inspection by the competent authorities.

Applicants are reminded that a qualified person is available to a manufacturing authorization holder according to Article 41 of Directive 2001/83/EC and Article 45 of Directive 2001/82/EC and located in the EU/EEA. Therefore, statements from personnel employed by manufacturers in third countries, including those located within the partner countries of the MoI, are not acceptable.

According to Article 46a (1) of Directive 2001/83/EC and Article 50a (1) of Directive 2001/82/EC, production includes the production, importation, separation, packaging or presentation in whole or in part before being incorporated into a medicinal product, including repackaging or reconstitution as performed by a distributor.

A statement is not required for blood or blood components subject to the requirements of Directive 2002/98/EC of the European Parliament and of the Council (1).

(1) OJ L 33, 8.2.2003, p. 30.

B.II.b.2 Change in importer, collection release arrangements and quality control testing of finished product	Conditions that are met	Documentation to be supplied	Type of procedure
a) Replacing or adding a place where the control / testing of the series is done	**2, 3, 4, 5**	**1, 2, 5**	**IA**
b) Substitution or addition of a place where batch control/testing takes place for a biological / immunological product and any test method performed at the place is a biological / immunological method			**II**
c) Replacement or addition of a manufacturer responsible for importing and/or releasing the series			
1. Not including batch control / testing	**1, 2,5**	**1, 2, 3, 4, 5**	**IA_{IN}**
2. Including batch control / testing	**1, 2, 3, 4, 5**	**1, 2, 3, 4, 5**	**IA_{IN}**
3. Involvement of batch control / testing for a biological / immunological product and any of the test methods performed at that place is a biological / immunological / immunochemical method			**II**

1.1.1.1.55 Conditions

1. The manufacturer responsible for the batch release must be within the EU / EEA. At least one batch release country remains within the EU/EEA that is able to validate product testing for the purpose of batch release within the EU/EEA.

2. The place is appropriately authorized.

3. The product is not a biological / immunological medicinal product.

4. The transfer of the method from the old place to the new place or new test laboratory has been successfully completed.

5. At least one control / batch testing place remains within the EU/EEA or in a country where there is an operational and appropriate MRA mutual recognition agreement between the relevant country and the EU, which is able to carry out product testing For the purpose of series release within the EU/EEA.

1.1.1.1.56 Documentation

1. For a country within the EU/EEA: Attach a copy of the production authorization or if there is no production authorization there is a GMP compliance certificate issued within the last 3 years by the relevant competent authority.

For a manufacturing country outside the EEA, where there is an operational MRA mutual recognition agreement between the country concerned and the EU: a GMP certificate, issued within the last 3 years by the relevant competent authority. Where no such agreement exists a GMP certificate issued within the last 3 years by a competent EU/EEA authority.

2. The variation application form must clearly describe the manufacturers, importers, batch control / testing and places of cumulative release of the 'present' and 'proposed' product as listed in section 2.5 of the marketing authorization application form.

3. For the centralized procedure only: contact details of the new EU/EEA contact person for defects and withdrawals, if applicable.

4. A statement from the Qualified Person (QP) responsible for batch certification stating that the manufacturers of the active substances mentioned in the marketing authorization act in accordance with the detailed guidelines for good manufacturing practices for the starting materials. A single statement may be acceptable under certain circumstances - see note under variation No B.II.b.1.

5 Amendment of relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.

B.II.b.3 Change in the production process of the finished product, including an intermediate used in the production of the finished product	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Small changes in the production process	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 3, 4, 5, 6, 7, 8**	**IA**
b) Substantial changes in a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product			**II**
c) The product is a biological / immunological medicinal product and the change requires a comparability assessment			**II**
d) Introduction of a non-standard terminal sterilization method			**II**
e) Presentation or growth of the over-age used for the active substance			**II**
f) Small changes in the production process of an oral aqueous suspension		**1, 2, 4, 6, 7,8**	**IB**

1.1.1.1.57 Conditions

1. No change in qualitative and quantitative impurity profile or physico-chemical properties.

2. Or the change concerns an immediate release solid oral dosage form / oral solution and the medicinal product in question is not a biological / immunological or herbal medicinal product;

   or the change is related to process parameters that in the context of a previous evaluation were considered not to have an impact on the quality of the finished product (regardless of the type of product and/or dosage form).

3. The manufacturing principle, including the single manufacturing steps, remain the same, e.g. processing intermediates and there are no changes in any manufacturing solvents used in the process.

4 The currently registered process must be controlled by the relevant controls in the process and no change (extension or deletion of limits) to these controls is required.

5. The specifications of the finished product or intermediates are unchanged.

6. The new process should lead to an identical product with respect to all aspects of quality, safety and efficiency.

7. Relevant stability studies in accordance with the relevant guidelines have been initiated with at least one pilot scale or industrial scale batch and at least 3 months of stability data are available to the applicant. It is ensured that these studies will be finalized and that the data will be immediately provided to the competent authorities if the external specifications or potential specifications outside are at the end of the approved deadline (with proposed action).

1.1.1.1.58 Documentation

1. Amendment of relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a direct comparison of the current process and the new process.

2. For semi-solid and liquid products in which the active substance is present in undissolved form: appropriate validation of the change including microscopic imaging of the particles to check for visible changes in morphology; Comparative data of size distribution by a convenient method.

3. For solid dosage forms: distribution profile data of a representative production batch and comparative data of the last three batches from the previous process; Data for the next two production batches should be available upon request or reported if specified externally (with proposed action). For herbal medicinal products, comparative dissolution data may be acceptable.

4. Reason for not submitting a new bioequivalence study according to relevant (human or veterinary) bioavailability guidelines.

5. For changes in process parameters that are considered not to have an impact on the quality of the finished product, the statement to this effect is reached in the context of the pre-approved risk assessment.

6. Copy of approved release specifications and release deadline.

7. Batch analysis data (in a comparative table format), on a minimum of one batch produced for both the approved and proposed processes. Collection data on two other production runs should be made available upon request and reported by the marketing authorization holder if external specifications (with proposed action).

8. Statement that the relevant stability studies have been initiated according to ICH/VICH conditions, as appropriate (with the indication of the batch numbers in question) and the relevant stability parameters have been evaluated in at least one pilot scale or industrial scale series and at least 3 months of satisfactory stability data are available to the applicant at the time of notification and that the stability profile is similar to the currently recorded situation. It is ensured that these studies will be finalized and that the data will be immediately provided to the competent authorities if the external specifications or potential specifications outside at the end of the

approved deadline (with proposed action).

B.II.b.4 Change in batch size (including batch size scales) of finished product	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Up to 10-times compared to the originally approved batch size	**1, 2, 3, 4, 5, 7**	**1, 4**	**IA**
b) Reduction up to 10-times	**1, 2, 3, 4, 5, 6**	**1, 4**	**IA**
c) The change requires the assessment of the comparability of a biological / immunological medicinal product or the change in the size of the pool requires a new bioequivalence study			**II**
d) The change is related to all other pharmaceutical forms produced by complex manufacturing processes			**II**

e) More than 10-times increase compared to the originally approved batch size for immediate-release (oral) pharmaceutical forms		**1, 2, 3, 4, 5, 6**	**IB**
f) The rate of a biological / immunological medicinal product is increased / decreased without changing the process (e.g. line doubling)		**1, 2, 3, 4, 5, 6**	**IB**

1.1.1.1.59 Conditions

1. The change does not affect the reproducibility and/or consistency of the product.
2. The change relates to conventional immediate-release oral pharmaceutical forms or non-sterile liquid-based pharmaceutical forms.
3. Any changes in the manufacturing method and/or in-process controls are only those required by the change in batch size, e.g. the use of devices of different sizes.
4. Validation scheme is in place or production validation has been successfully performed according to the current protocol with at least three batches at the proposed new batch size in accordance with the relevant guidelines.
5. The product in question is not a biological / immunological medicinal product.
6. The change must not be the result of unexpected events occurring during production or due to stability concerns.
7. The batch size is within the range of ten times the batch size envisaged when the marketing authorization was granted or after a subsequent variation was not agreed as a type IA variant.

1.1.1.1.60 DOCUMENTATION

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.
2. Batch analysis data (in a comparison table format) on a minimum of one production batch produced for both currently approved and proposed sizes. Batch data on the two batch batches of future production should be made available upon request and reported by the MAH if external specifications (with proposed action).
3. Copy of approved release specifications and expiration dates.
4. When relevant, the batch numbers, corresponding batch size and production date of the batches (≥ 3) used in the validation study should be indicated or the validation protocols (schemes) submitted.
5. Validation results should be provided

6. The results of stability studies carried out according to ICH/VICH conditions, on the relevant stability parameters, in at least one pilot or industrial group, covering a minimum period of 3 months and an assurance is given that these studies will be finalized and these data will be immediately provided to the competent authorities if they are out of specification or potentially out of specification at the end of the approved period (with proposed action). For biologics/immunologies: a statement that a comparability assessment is not required.

B.II.b.5 Change in in-process tests or limits applied during production of the finished product	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Tightening the borders in the process	**1, 2, 3, 4**	**1, 2**	**IA**
b) Adding new tests and limits	**1, 2, 5, 6**	**1, 2, 3, 4, 5, 7**	**IA**
c) Deleting an irrelevant test in the process	**1, 2, 7**	**1, 2, 6**	**IA**

d) Deleting an in-process test that may have a significant effect on the overall quality of the finished product			**II**
e) Extending the approved IPC limits, which may have a significant effect on the overall quality of the finished product			**II**
f) Adding or replacing a test in the process as a result of a safety or quality problem		**1, 2, 3, 4, 5, 7**	**IB**

1.1.1.1.61 Conditions

1. The change is not a consequence of any commitment from previous evaluations to review the specification limits (e.g, made during the procedure for the application for marketing authorization or for a type II variation procedure).

2. The change does not come from unexpected events that arise during production, e.g. unqualified new dirt; change in total impurity limits.

3. Any changes must be within the currently approved limits.

4. The test procedure remains the same, or the changes in the test procedure are minor.

5. Any new test method does not involve a new non-standard technique or a standard technique used in a new way.

6. The new test method is not a biological / immunological / immunochemical method or a method that uses a biological reagent for a biologically active substance (does not include standard pharmacopoeial microbiological methods).

7. The in-process test is not concerned with the control of a

   critical parameter, e.g:

   analysis,

   impurities (unless a special solvent is definitely not used in

   production)

   any critical physical characteristics (particle size, bulk, bulk density,

   etc.)

identity test (unless there is a suitable alternative control already present)

microbiological control (if not required for the particular dosage form)

1.1.1.1.62 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

2. Comparison table of current and proposed in-process tests and limits.

3. Details of any new analytical methods and validation data, where appropriate.

4. Batch analysis data on two production runs (3 production runs for biologics, unless otherwise justified) of the finished product for all specification parameters.

5. When appropriate, comparative distribution profile data for the finished product in at least one pilot batch produced using current and new in-process tests. For herbal medicinal products, comparative collection data may be acceptable.

6 Rationale/risk assessment indicating that the in-process test is not relevant or is outdated.

7. Justification of the new test in process and limits.

B.II.c) *Control of excipients*

B.II.c.1 Change in the specification parameters and / or limits of an excipient	Conditions that are met	Documentation to be supplied	Type of procedure
a) Tightening the specification limits	1, 2, 3, 4	1, 2	IA
b) Adding a new specification parameter to the specification with the corresponding test method	1, 2, 5, 6, 7	1, 2, 3, 4, 6, 8	IA
c) Deleting an unimportant specification parameter (e.g. deleting an obsolete parameter)	1, 2, 8	1, 2, 7	IA
d) Change out of the limits of the approved specifications			II co n
e) Deleting a specification parameter that may have a significant effect on the overall quality of the finished product			II n d
f) Addition or replacement (except for biological or immunological product) of a specification parameter with the corresponding test method as a result of a safety or quality problem		1, 2, 3, 4, 5, 6, 8	IB
g) When there is no monography in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the excipient, a change in the description of the preparation from home to a non-official Phar macopera or a Pharmacopoeia of a third country		1, 2, 3, 4, 5, 6, 8	IB

1.1.1.1.63 Conditions

1. The change is not a consequence of any commitment from previous evaluations to review the specification limits (eg, made during the procedure for the application for marketing authorization or for a type II variation procedure).

2. The change does not come from unexpected events that arise during production, e.g. unqualified new dirt; change in total impurity limits.

3. Any changes must be within the currently approved limits.

4. The test procedure remains the same, or the changes in the test procedure are minor.

5. Any new test method does not involve a new non-standard technique or a standard technique used in a new way.

6. The test method is not a biological / immunological / immunochemical method, or a method that uses a biological reagent (does not include standard pharmacopoeial microbiological methods)

7. The change has nothing to do with genotoxic dirt.

8. The specification parameter is not about controlling a critical parameter, e.g:

   impurities (unless a special solvent is definitely not used in the manufacture of the excipient)

   any critical physical characteristics (particle size, bulk, bulk density, etc.)

   identity test (unless a suitable alternative check already exists)

   microbiological control (if not required for the particular dosage form)

1.1.1.1.64 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

2. Comparison table of current and proposed specifications.

3. Details of any new analytical methods and validation data, where appropriate.

4. Batch analysis data on two production batches (3 production batches for biological excipients) of the excipient for all specification parameters.

5. When appropriate, comparative distribution profile data for the finished product in at least one pilot batch containing the excipient conforming to the current and proposed specifications. comparative dissolution data may be acceptable for herbal medicinal products.

6. Justification for not submitting a new bioequivalence study according to the relevant (Human, Veterinary) Bioavailability Guidelines, if appropriate.

7. Rationale/risk assessment indicating that the in-process test is not relevant or is out of date.

8. Justification of the new specification parameter and limits.

B.II.c.2 Change in test procedure for an excipient	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Minor changes to an approved test procedure	**1, 2, 3, 4**	**1, 2**	**IA**
b) Deleting a test procedure if an alternative test procedure is already authorized	**5**	**1**	**IA**
c) Substantial change or replacement of the biological / immunological / immunochemical test method or a method that uses a biological reagent			**II**
d) Other changes in a test process (including replacement or addition)		**1, 2**	**IB**

1.1.1.1.65 Conditions

1. Adequate validation studies have been performed in accordance with relevant guidelines and demonstrate that the updated test procedure is at least equivalent to the previous test procedure.

2. There were no changes in total impurity limits; no new unqualified impurities are detected.

3. The method of analysis must remain the same (e.g. a change in column length or temperature, but not a different column or method).

4. The test method is not a biological / immunological / immunochemical method or a method using a biological reagent (does not include standard microbiological pharmacopoeial methods).

5. An alternative test procedure is already authorized for the specification parameters and this procedure has not been added through the IA/IA (IN) notification.

1.1.1.1.66 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate, including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).

2. The results of the comparative evaluation or if the results of the justified comparative analysis show that the actual test and the proposal are equivalent. This requirement is not applicable in case of adding a new test procedure.

B.II.c.3 Change in the source of an excipient or reagent with a TSE risk	Conditions that are met	Documentation to be supplied	Type of procedure
a) From TSE risk material to plant or synthetic origin			
1. For excipients or reagents that are not used in the production of a biological / immunological active substance or in a biological / immunological medicinal product	1	1	IA
2. For excipients or reagents used in the manufacture of a biological / immunological active substance or in a biological / immunological medicinal product		1, 2	IB
b) Changing or inserting TSE risk material or replacing a TSE risk material by a TSE risk material which is not covered by a TSE certificate of suitability			II d m en

1.1.1.1.67 Conditions

1. Excipient and finished product release and shelf life specifications remain the same.

1.1.1.1.68 Documentation

1. Statement by the producer or marketing authorization holder of the material that it is pure of plant or synthetic origin.

2. Study of the equivalence of materials and the impact on the production of the final material and the impact on the behavior (e.g. dissolution characteristics) of the finished product.

B.II.c.4 Change in the synthesis or recovery of a non-pharmacopoeial excipient (when described in the file) or a new excipient	Conditions that are met	Documentation to be supplied	Type of procedure
a) Minor changes in the synthesis or recovery of a non-pharmacopoeial excipient or a new excipient	1, 2	1, 2, 3, 4	IA
b) The specifications are affected or there is a change in the physico-chemical properties of the excipient that may affect the quality of the finished product.			II d m en
c) The excipient is a biological / immunological substance			II

1.1.1.1.69 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 ICH/VICH limits) or physicochemical properties.

2. Adjuvants are excluded.

1.1.1.1.70 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

2. Batch analysis data (in a comparative tabular format) of at least two batches (minimum pilot scale) of the excipient produced by the old and new process.

3. Where appropriate, comparative distribution profile data for the finished product of at least two batches (minimum pilot scale). For herbal medicinal products, comparative dissolution data may be acceptable.

4. Copy of the approved and new (if applicable) specifications of the excipient.

B.II.d) *Control of the finished product*

B.II.d.1 Change in the specification parameters and / or limits of the finished product	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Tightening the specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Tightening the specification limits for medicinal products subject to the Official Authorization of the Control Authority	**1, 2, 3, 4**	**1, 2**	**IA_{IN}**
c) Adding a new specification parameter to the specification with the corresponding test method	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 7**	**IA**
d) Deletion of a non-relevant specification parameter (e.g. deletion of an obsolete parameter such as aroma and taste or identification test for a coloring or flavoring)	**1, 2, 9**	**1, 2, 6**	**IA**
e) Change outside the limits of the approved specifications			**II**
f) Deletion of a specification parameter that may have a significant effect on the overall quality of the finished product			**II n d**
g) Addition or replacement (except for the biological or immunological product) of the specification parameter with the corresponding test method as a result of a safety or quality problem		**1, 2, 3, 4, 5, 7**	**IB**
h) Updating the file in accordance with the provisions of an updated general Ph Eur monograph for the finished product(*)	**1, 2, 3, 4, 7, 8**	**1, 2**	**IA_{IN}**
i) Ph Eur. 2.9.40 Uniformity of dosage units is introduced to replace the currently registered method, or Ph. Eur. 2.9.5 (Uniformity of mass) or Ph. Eur. 2.9.6 (Content uniformity)	**1, 2, 10**	**1, 2, 4**	**IA**

1.1.1.1.71 Conditions

1. The change is not a consequence of any commitment from previous assessments to review the specification limits (e.g., made during the marketing authorization

application procedure or type II variation procedure), unless the supporting documentation has already been assessed and approved within another procedure.

2. The change does not come from unexpected events that arise during production, e.g. unqualified young dirt; change in total impurity limits.

3. Any changes must be within the currently approved limits.

4. The test procedure remains the same, or the changes in the test procedure are minor.

5. Any new test method does not involve a new non-standard technique or a standard technique used in a new way.

6. The test method is not a biological / immunological / immunochemical method or a method that uses a biological reagent for a biologically active substance.

7. The change is not related to any impurities (including genotoxicity) or decomposition.

8. The change is about updating the microbial control limits to be in line with the current Pharmacopoeia and the microbial control limits currently registered (current state) are in line with the state before January 2008 (not harmonized) and do not include any additional controls specified on the requirements of the Pharmacopoeia for the particular dosage form and the proposed controls are in accordance with the harmonized monograph.

9. The specification parameter or proposal for the specific dosage form does not concern a critical parameter e.g.:

   analysis,

   impurities (unless a special solvent is definitely not used in the production of the

   finished product) any critical physical characteristics (hardness or stiffness for

   uncoated tablets, size, etc.)

   a test required for the particular dosage form in accordance with the general notices

   of Ph. Eur.;

   any test skip (random) requests.

10. The proposed control is fully compliant with Table 2.9.40.-1 of Ph. Eur. 2.9.40 monograph, and does not include the alternative proposal for testing the uniformity of dosage units according to Mass Variation instead of Content Uniformity when the latter is specified in Table 2.9.40.-1.

1.1.1.1.72 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

2. Comparison table of current and proposed specifications.

3. Details of any new analytical methods and validation data, where appropriate.

4. Batch analysis data on two production runs (3 production runs for biologics, unless otherwise justified) of the finished product for all specification parameters

5. Where appropriate, comparative distribution profile data for the finished product in at least one pilot batch conforming to the current and proposed specifications. For herbal medicinal products, comparative collection data may be acceptable.

6 Rationale/risk assessment indicating that the in-process test is not relevant or is out of date.

7. Justification of the new specification parameter and limits

---

(*) Note: There is no need to notify the competent authorities of an updated monograph of the European Pharmacopoeia or a national pharmacopoeia of a Member State in case the reference is made to the 'current edition' in the file of an authorized medicinal product. This variation applies, therefore, to cases where there is no reference to the updated monograph of the pharmacopoeia included in the technical file and the change is made to refer to the updated version.

B.II.d.2 Change in the test procedure for the finished product	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Minor changes to an approved test procedure	**1, 2, 3, 4,**	**1,2**	**IA**
b) Deleting a test procedure if an alternative method is already authorized	**4**	**1**	**IA**

c) Substantial change in or replacement of the 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 en t**
d) Other changes in a test process (including replacement or addition)		**1, 2**	**IB**
e) Updating the testing procedure in accordance with the updated general monograph in Ph Eur.	**2, 3, 4, 5**	**1**	**IA**
f) To reflect compliance with the Ph.Eur. And to remove the reference to the old internal test method and test method number(*)	**2, 3, 4, 5**	**1**	**IA**

1.1.1.1.73 Conditions

1. Adequate validation studies have been performed in accordance with relevant guidelines and demonstrate that the updated test procedure is at least equivalent to the previous test procedure.

2. There were no changes in total impurity limits; no new unqualified impurities are detected

3. The method of analysis must remain the same (e.g. a change in column length or temperature, but not a different column or method);

4. The test method is not a biological / immunological / immunochemical method or a method using a biological reagent (does not include standard microbiological pharmacopoeial methods).

5. The test procedure already recorded refers to the general monograph of Ph. Eur. and each change is minor in nature and requires updating the technical file.

1.1.1.1.74 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate, including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).

2. The results of the comparative validity or if the results of the justified comparative analysis show that the current test and the proposed one are equivalent; This requirement is not applicable in case of adding a new test procedure.

(*) *Note:* There is no need to notify the competent authorities of an updated monograph of the European Pharmacopoeia in case the reference is made to the 'current edition' in the file of an authorized medicinal product.

B.II.d.3 Variations related to the introduction of real-time release or parametric release in the production of the finished product	Conditions that are met	Documentation to be supplied	Type of procedure
			of se

B.II.e) *Container closure system*

B.II.e.1 Change in the immediate packaging of the finished product	Conditions that are met	Documentation to be supplied	Type of procedure
a) Qualitative and quantitative composition			
1. Solid pharmaceutical form	**1, 2, 3**	**1, 2, 3, 4, 6**	**IA**

2. Semi-solid and non-sterile liquid pharmaceutical forms		**1, 2, 3, 5, 6**	**IB**
3. Sterile medicinal products and biological / immunological medicinal products.			**II** **on** **d**
4. The change is related to a less protective package where there are related changes to the Storage Conditions and/or reduction of the storage period.			**II** **n** **d**
b) Changing the type of container or adding a new container			
1. Semi-solid and non-sterile solid pharmaceutical forms		**1, 2, 3, 5, 6, 7**	**IB**
2. Sterile medicinal products and biological / immunological medicinal products			**II** **co** **n**
3. Deletion of an immediate packaging container that does not lead to complete deletion of the pharmaceutical strength or form	**4**	**1, 8**	**IA**

1.1.1.1.75 Conditions

1. The change only concerns the same type of packaging / container (e.g.blister to blister).

2. The proposed packaging material must be at least equivalent to the approved material in terms of its respective properties.

3. Relevant stability studies have been initiated according to ICH/VICH conditions and relevant stability parameters have been evaluated in at least two pilot batches or industrial scale and at least 3 months of stable stability data are available to the applicant at the time of application. However, if the proposed packaging is more resistant than the existing packaging, e.g. Thicker blister pack, 3 months stability data not yet available. These studies must be finalized and the data will be provided immediately to the competent authorities if the specifications out or potential specifications out at the end of the approved deadline (with proposed action).

4. The remaining product presentations should be suitable for the dosage instructions and duration of treatment as mentioned in the summary of product characteristics.

1.1.1.1.76 Documentation

1. Amendment of relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate, including revised product information as appropriate.

2. Data suitable for new packaging (comparative data on permeability, e.g. humidity. for O2, of CO2).

3. When appropriate, evidence should be provided that there is no interaction

between the contents and the packaging material (e.g. no migration of components of the proposed material into the contents and no loss of product components into the packaging), including confirmation that the Material is in accordance with the relevant pharmacopoeial requirements or Union legislation on plastic materials and objects in contact with food.

4. A statement that the necessary stability studies have been initiated under ICH/VICH conditions (marking the relevant batch numbers) and that, as necessary, the minimum required stability data were available to the applicant at the time of application and that the data available do not show any problems. It must also be ensured that the studies will be finalized and that the data will be immediately provided to the competent authorities if the external specifications or potential specifications outside at the end of the approved deadline (with proposed action).

5. The results of stability studies that have been carried out according to ICH/VICH conditions, on the relevant stability parameters, in at least two pilot or industrial groups, covering a minimum period of 3 months and an assurance has been given that these studies will be finalized and these data will be immediately provided to the competent authorities if the specifications out or potential specifications out at the end of the approved period (with proposed action).

6. Comparison table of current and proposed immediate packaging specifications, if applicable.

7. Samples of the new container / closure where applicable (see NTA, Sample requirements in Member States/ EMA).

8. Statement that the size of the remaining packages is/are consistent with the dosing regimen and duration of treatment and suitable for the dosing instructions as approved in the summary of product characteristics.

Note: for B.II.e.1.b), applicants are reminded that any change resulting in a "new pharmaceutical form" requires submission of an extension application.

B.II.e.2 Change in the specification parameters and / or limits of immediate packaging of the finished product	Conditions that are met	Documentation to be supplied	Type of procedure
a) Tightening the specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Adding a new specification parameter to the specification with the corresponding test method	**1, 2, 5**	**1, 2, 3, 4, 6**	**IA**
c) Deleting an unimportant specification parameter (e.g. deleting an obsolete parameter)	**1, 2**	**1, 2, 5**	**IA**
d) Adding or replacing a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4, 6**	**IB**

1.1.1.1.77 Conditions

1. The change is not a consequence of any commitment from previous evaluations to review the specification limits (e.g, made during the procedure for the application for marketing authorization or for a type II variation procedure).

2. The change does not result from unexpected events that arise during production.

3. Any changes must be within the currently approved limits.

4. The test procedure remains the same, or the changes in the test procedure are minor.

5. Any new test method does not involve a new non-standard technique or a standard technique used in a new way

1.1.1.1.78 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

2. Comparison table of current and proposed specifications.

3. Details of any new analytical methods and validation data, where appropriate.

4. Series analysis data in two sets of immediate packaging for all specification parameters.

5. Rationale/risk assessment indicating that the in-process test is not relevant or is out of date.

6. Justification of the new specification parameter and limits.

B.II.e.3 Change in the test procedure for the immediate packaging of the finished product	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Minor changes to an approved test procedure	**1, 2, 3**	**1, 2**	**IA**

b) Other changes to a test process (including replacement or addition)	**1, 3, 4**	**1, 2**	**IA**
c) Deleting a test procedure if an alternative test procedure is already authorized	**5**	**1**	**IA**

1.1.1.1.79 Conditions

1. Adequate validation studies have been performed in accordance with relevant guidelines and validation studies show that the updated test procedure is at least equivalent to the previous test procedure.
2. The method of analysis must remain the same (e.g. a change in column length or temperature, but not a different column or method).
3. Any new test method does not involve a new non-standard technique or a standard technique used in a new way.
4. The active substance / finished product is not biological / immunological.
5. An alternative test procedure is already authorized for the specification parameters and this procedure has not been added through the IA/IA (IN) notification.

1.1.1.1.80 Documentation

1. Amendment of relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate, including a description of the analytical methodology, a summary of the validation data.
2. The results of the comparative evaluation or if the results of the justified comparative analysis show that the actual test and the proposal are equivalent. This requirement is not applicable in case of adding a new test procedure.

B.II.e.4 Change in shape or size of container or closure (immediate packaging)	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Non-sterile medicinal products	**1, 2, 3**	**1, 2, 4**	**IA**
b) The change in shape or size concerns a fundamental part of the packaging material, which may have a significant impact on the distribution, use, safety or stability of the finished product			**II d m en**
c) Sterile medicinal products		**1, 2, 3, 4**	**IB**

1.1.1.1.81 Conditions

1. There is no change in the qualitative or quantitative composition of the container.
2. The change does not involve a fundamental part of the packaging material, which

affects the distribution, use, safety or stability of the finished product.

3. In case of a change in the opening space or a change in the surface / volume ratio, stability studies in accordance with the relevant guidelines have been initiated and the relevant stability parameters have been evaluated in at least two pilot scales (three for biological / immunological medicinal products) or batches on an industrial scale and at least 3 months (6 months for biological / immunological medicinal products) stability data are available to the applicant. It is ensured that these studies will be finalized and that the data will be provided immediately to the competent authorities if the specifications are out or the external specifications are out of use at the end of the approved period (with proposed action).

1.1.1.1.82 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA 6B format for veterinary products, as appropriate), including the description, detailed drawing and composition of the container or closure material, and including the revised product information as per case.

2. Samples of the new container / closure where applicable (see NTA, Sample Requirements in Member States).

3. Revalidation studies are performed in the case of terminally sterilized sterile products. Batch numbers of batches used in revalidation studies should be indicated where applicable.

4. In case of a change in the opening space or a change in the surface / volume ratio, a statement that the required stability studies have been initiated according to ICH/VICH conditions (with the sign of the relevant series numbers) and that, Minimum data required stability data were available to the applicant at the time of implementation for a Type IA notification and at the time of submission of a Type IB notification and that the available data did not indicate any problems. It must also be ensured that the studies will be finalized and that the data will be immediately provided to the competent authorities if the external specifications or possible specifications outside at the end of the approved period (with proposed action).

B.II.e.5 Change in the packaging size of the finished product	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Change in the number of units (e.g. tablets, ampoules, etc.) in a package			
1. Change within the range of currently approved package sizes	**1, 2**	**1, 3**	**IA_{IN}**
2. Change outside the scope of currently approved package sizes		**1, 2, 3**	**IB**
b) Deletion of package sizes	**3**	**1, 2**	**IA**
c) Change in filling volume / sterility (or with one dose, partial use) of parenteral medicinal products, including biological / immunological medicinal products			**II m en t**
d) Change in fill volume / filling volume of multi-dose non-parenteral products (or single-dose, fractional use)		**1, 2, 3**	**IB**

1.1.1.1.83 Conditions

1. The new package size must be consistent with the dosage and duration of treatment approved in the Summary of Product Characteristics.

2. The primary packaging material remains the same.

3. The remaining product presentations should be suitable for the dosage instructions and duration of treatment as mentioned in the Summary of Product Characteristics.

1.1.1.1.84 Documentation

1. Amendment of relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate including revised product information as appropriate.

2. Justification for the new/remaining pack size, indicating that the new/remaining size is/are compatible with the dosage regimen and duration of treatment approved in the summary of product characteristics

3. Statement that stability studies will be carried out in accordance with the relevant guidelines for products where stability parameters may be affected. Data should only be reported if external specifications (with proposed action).

*Note:*for B.II.e.5.c) and d), applicants are reminded that any change in the "strength" of the medicinal product requires the submission of an extension application.

B.II.e.6 Change in any part of the (primary) packaging material that is not in contact with the finished product form (such as the color of the flip-tops, the color-coded rings on the ampoules, the change of the shield needles (other plastic is used)	Conditions that are met	Documentation to be supplied	Type of procedure
a) Change affecting product information	1	1	IA_{IN}
b) Change that does not affect product information	1	1	IA

1.1.1.1.85 Conditions

1. The change does not concern a part of the packaging material, which affects the distribution, use, safety or stability of the finished product.

1.1.1.1.86 Documentation

1. Amendment of relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.

B.II.e.7 Change in supplier of packaging components or equipment (when mentioned in the file)	Conditions that are met	Documentation to be supplied	Type of procedure
a) Deleting a supplier	1	1	IA
b) Replacing or adding a supplier	1, 2, 3, 4	1, 2, 3	IA
c) Any change in suppliers of spacer devices for metered dose inhalers			II co

1.1.1.1.87 Conditions

1. No deletion of component or packaging device.
2. The qualitative and quantitative composition of the packaging / device components and design specifications remain the same.
3. The specifications and quality control method are at least equivalent.
4. The sterilization method and conditions remain the same, if applicable.

1.1.1.1.88 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

2. For devices for medicinal products for human use, proof of CE marking.

3. Comparison table of current and proposed specifications, if applicable.

B.II.f) *Stability*

B.II.f.1 Change in the terms of storage or storage of the finished product	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Reduction of the shelf life of the finished product			
1. As packaged for sale	**1**	**1, 2, 3**	**IA_{IN}**

2. After the first opening	**1**	**1, 2, 3**	**IA_{IN}**
3. After thinning or reconstruction	**1**	**1, 2, 3**	**IA_{IN}**
b) Extending the shelf life of the finished product			
1. As packaged for sale (backed by real-time data)		**1, 2, 3**	**IB**
2. After first opening (backed by real-time data)		**1, 2, 3**	**IB**
3. After dilution or reconstruction (supported by real-time data)		**1, 2, 3**	**IB**
4. Extending the shelf life based on additional stability information is inconsistent with ICH / VICH guidelines(*)			**II**
5. Extending the shelf life of the biological / immunological medicinal product in accordance with an approved stability protocol.		**1, 2, 3**	**IB**
c) Change in storage conditions for biological medicinal products, when stability studies have not been performed in accordance with an approved stability protocol			**II**
d) Changing the storage conditions of the finished product or the diluted/reconstituted product		**1, 2, 3**	**IB**
e) Change in an approved stability protocol	**1, 2**	**1, 4**	**IA**

1.1.1.1.89 Conditions

1. The change must not be the result of unexpected events occurring during production or due to stability concerns.

2. The change does not concern the expansion of the acceptance criteria in the tested parameters, the removal of stability indicating parameters or a reduction in the frequency of testing.

1.1.1.1.90 Documentation

1. Amendment of relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate). This should contain the results of appropriate real-time stability studies (covering the entire storage period) carried out in accordance with the relevant stability guidelines for at least two pilot batches (1) of the finished product in the packaging material of authorized and / or after the first opening Or reconstitution, as the case may be; Where possible, the results of appropriate microbiological testing should be included.

2. Revised product information

3. The last approved copy of the expiry period of the finished product and when applicable, the specifications after dilution / reconstitution or first opening.

4. Justification for proposed changes.

(*) *Note*: extrapolation does not apply to the biological / immunological medicinal product.

(1) Pilot-scale batches may be accepted with a commitment to verify longevity in production-scale batches.

B.II.g) *Space change management protocol and post-approval*

B.II.g.1 Introduction of a new design space or expansion of the approved design space for the finished product, in relation to:	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) One or more unit operations in the manufacturing process of the finished product including in-process controls and/or testing procedures		**1, 2, 3**	**IIdme nt**
b) Test procedures for excipients / intermediates and / or finished product.		**1, 2, 3**	**IIo nd me**

1.1.1.1.91 Documentation

1. Results from product and process development studies (including risk assessment and multivariate studies, as appropriate) demonstrating that a systematic mechanistic understanding of material attributes and process parameters to critical quality attributes of the finished product has been achieved.

2. Description of the design space in tabular form, including variables (material attributes and process parameters, as appropriate) and their proposed ranges.

3. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

B.II.g.2 Implementation of a post-approval change management protocol related to the finished product	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
		1, 2, 3	**II**

1.1.1.1.92 Documentation

1. Detailed description of the proposed change.

2. Change management protocol regarding the finished product.

3. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volue 6B for veterinary products, as appropriate.

B.II.g.3 Deletion of an approved change management protocol related to the finished product	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
	1	**1, 2**	**IA_{IN}**

1.1.1.1.93 Conditions

1. Deletion of the approved change management protocol related to the end product is not the result of unexpected events or specified results during the

implementation of the changes described in the protocol and do not have any effect on the information already approved in the file.

1.1.1.1.94 Documentation

1. Reason for proposed deletion.

2. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.

B.II.g.4 Changes to an approved change management protocol	Conditions that are met	Documentation to be supplied	Type of procedure
a) Major changes to an approved change management protocol			**II on d**

b) Minor changes to an approved change management protocol that do not change the strategy defined in the protocol		**1**	**IB**

1.1.1.1.95 Documentation

1. Stating that any changes must be within the currently approved limits. In addition, the statement that a comparability assessment is not required for biological / immunological medicinal products.

B.II.g.5 Implementation of changes provided for in an approved change management protocol	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Implementation of the change does not require further supporting data	**1**	**1, 2, 4**	**IA_{IN}**
b) Implementation of the change requires further supporting data		**1, 2, 3, 4**	**IB**
c) Implementation of a change for a biological / immunological medicinal product		**1, 2, 3, 4, 5**	**IB**

1.1.1.1.96 Conditions

1. The proposed change is made in full compliance with the approved change management protocol, which requires immediate notification upon implementation.

1.1.1.1.97 Documentation

1. Reference to approved change management protocol.
2. Statement that the change is consistent with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, the statement that a comparability assessment is not required for biological / immunological medicinal products.
3. Results of studies conducted in accordance with the approved change management protocol.
4. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.
5. Copy of approved finished product specifications.

B.II.h.1 Update information 'Security Assessment of Case Agents' (section 3.2.A.2)	Conditions that are met	Documentation to be supplied	Type of procedure
a) Studies related to production steps studied for the first time for one or more random agents			**II t**
b) Replacement of outdated studies related to fabrication steps and case agents presented in the file			
1) with the modification of the risk assessment			**II**
2) without modifying the risk assessment		**1, 2, 3**	**IB**

1.1.1.1.98 Documentation

1. Amendment of the relevant sections of the files including the introduction of new studies to investigate the ability of manufacturing steps to deactivate / reduce incidental agents.

2. Reasoning that studies do not change risk assessment.

3. Changing product information (where applicable).

B.III MONOGRAPHS/CEP/TSE

B.III.1 Submission of a Ph. Certificate. Eur. of eligibility or deletion of the Ph. Certificate. Eur. of suitability:	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
For an active substance **For a starting material / reagent / intermediate used in the production process of the active substance** **For an excipient**			
a) European Pharmacopoeia Certificate of Conformity with Ph Eur. Monograph.			
1. New certificate from an already approved manufacturer	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA_{IN}**
2.Updated certificate from an already approved manufacturer	**1, 2, 3, 4, 8**	**1, 2, 3, 4, 5**	**IA**
3.New certificate from a new manufacturer (replacement or addition)	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA_{IN}**
4.Deletion of certificates (in case there are multiple certificates for material)	**10**	**3**	**IA**
5.New certificate for a non-sterile active substance to be used in a sterile medicinal product where water is used in the final steps of synthesis and the material is not claimed to be endotoxin free		**1, 2, 3, 4, 5, 6**	**IB**
b) TSE European pharmacopoeia certificate of suitability for the active substance / starting material / reagent / intermediate / or excipient			
1.New certificate for an active substance from a new manufacturer or an already approved manufacturer	**3, 5, 6, 11**	**1, 2, 3, 4, 5**	**IA_{IN}**
2.New certificate for a starting material / reagent / intermediate / or supplement from a new manufacturer or an already approved manufacturer	**3, 6, 9**	**1, 2, 3, 4, 5**	**IA**
3.Updated certificate from an already approved manufacturer	**7, 9**	**1, 2, 3, 4, 5**	**IA**
4.Deletion of certificates (in case there are multiple certificates for material)	**10**	**3**	**IA**

5. New / updated certificate from an already approved / new manufacturer using materials of human or animal origin for which a risk assessment is required regarding potential contamination with accidental agents			**II en t**

1.1.1.1.99 Conditions

1. Final product release and shelf life specifications remain the same.
2. Unchanged (excluding crimping) additional specifications (for Ph. Eur.) for impurities (excluding residual solvents, provided they are ICH/VICH compliant) and product specific requirements (e.g. size profiles particulate, polymorphic form) if applicable.
3. The production process of the active substance, starting material / reagent / intermediate does not involve the use of materials of human or animal origin, for which an evaluation of viral safety data is required.
4. For the active substance only, it will be tested immediately before use, unless the testing period for the Ph. Eur Eligibility Certificate is included . or if data to support a trial period are not already provided on the file.
5. Active substance / starting material / reagent / intermediate / excipient is not sterile.
6. The substance is not included in a veterinary medicinal product for use in animal species susceptible to TSE
7. For veterinary medicinal products: there was no change in the source of the material.
8. For herbal active substances: production route, physical form, extraction solvent and drug extract ratio (RED) should remain the same.
9. If gelatin produced from bone is to be used in a medicinal product for parenteral use, it should only be produced in accordance with relevant country requirements.
10. At least one manufacturer for the same substance remains on the file.
11. If the active substance is not a sterile substance, but must be used in a sterile medicinal product, then according to the CEP it must not use water during the last steps of synthesis or if the active substance must be obtained it must be free of bacterial endotoxin.

1.1.1.1.100 Documentation

1. Current (updated) copy of Eligibility Certificate Ph. Eur.
2. In case of adding a manufacturing site, the Change Application Form must clearly

describe the "present" and "proposed" manufacturers as listed in section 2.5 of the application form.

3. Amendment of relevant sections of the file (submitted in EU-CTD format).

4. Where possible, a document providing information on any material included in the scope of the Guidance *Note for Minimizing the Risk of Transmission of Mammalian Spongiform Disease Agents through Human and Veterinary* Medicinal Products including those used in the manufacture of the active substance / excipient. For each such material the following information must be included: manufacturer's name, species and tissues from which the material is derived, country of origin of the source animal and its use.

   For the Centralized procedure, this information must be included in an updated TSE table A (and B, if relevant).

5. Where applicable, for the active substance, a statement from the qualified person (QP) of each of the manufacturing authorization holders listed in the application where the active substance is used as starting material and a statement from the QP of each of the manufacturers listed on the application as responsible for release from collection. These statements must state that the manufacturers of the active substances mentioned in the application act in accordance with detailed guidelines for good manufacturing practices for starting materials. A single statement may be acceptable in certain circumstances - see note under amendment no. B.II.b.1. The production of intermediates also requires a QP statement, while as regards certificate updates for active substances and intermediates,

6. Appropriate evidence to confirm the compliance of the water used in the last steps of the synthesis of the active substance with the relevant requirements on the quality of water for pharmaceutical use.

B.III.2 Change in accordance with Ph Eur. or with a national pharmacopoeia of a Member State	Conditions that are met	Documentation to be supplied	Type of procedure
a) Changing the specifications of a previous EU non-pharmaceutical substance in full compliance with Ph. Eur. or with a national pharmacopoeia of a Member State			
1. Active substance	**1, 2, 3, 4, 5**	**1, 2, 3, 4**	**IA_{IN}**
2. Starting material of the excipient/active substance	**1, 2, 4**	**1, 2, 3, 4**	**IA**
b) Change in accordance with an update of the corresponding Ph. monograph. Eur. or the national pharmacopoeia of a Member State	**1, 2, 4, 5**	**1, 2, 3, 4**	**IA**
c) Change in specifications from a national pharmacopoeia of a Member State to Ph. Eur.	**1, 4, 5**	**1, 2, 3, 4**	**IA**

1.1.1.1.101 Conditions

1. The change is made exclusively in full compliance with the pharmacopoeia. All tests in the specification must correspond to the pharmacopoeial standard after the change, with the exception of additional supplementary tests.
2. Additional pharmacopoeia specifications for specific product properties are unchanged (e.g. particle size profiles, polymorphic forms or, /e.g biocones, aggregates).
3. There are no significant changes in the qualitative and quantitative profile of impurities unless the specifications are tightened
4. Additional validation of a new or changed pharmacopoeial method is not necessary
5. For herbal active substances: production route, physical form, extraction solvent and drug extract ratio (RED) should remain the same.

1.1.1.1.102 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.
2. Comparison table of current and proposed specifications.

3. Batch analysis data (in a comparative tabular format) on the two production batches of the relevant substance for all tests in the new specification and in addition, where appropriate, comparative distribution profile data for the finished product in at least one pilot series. For herbal medicinal products, comparative dissolution data may be acceptable.

4. Data to demonstrate the suitability of the monograph to control the substance, e.g. a comparison of possible impurities with the transparency note of the monograph.

Note: There is no need to notify the competent authorities of an updated monograph of the European Pharmacopoeia or a national pharmacopoeia of a Member State in case reference is made to the 'current edition' in the file of an authorized medicinal product.

B.IV MEDICAL DEVICES

B.IV.1 Changing a measuring or administration device	Conditions that are met	Documentation to be supplied	Type of procedure
a) Adding or replacing a device that is not an integrated part of the primary packaging			
1. CE marked device	**1, 2, 3, 6, 7**	**1, 2, 4**	**IA_{IN}**
2. Device without CE mark for veterinary products only		**1, 3, 4**	**IB**
3. Distance device for metered dose inhalers or other devices that may have a significant impact on the distribution of the active substance in the product (e.g. nebulizers)			**II**
b) Deleting a device	**4, 5**	**1, 5**	**IA_{IN}**
c) Addition or replacement of a device that is an integrated part of the primary packaging			**II**

1.1.1.1.103 Conditions

1. The proposed measuring or administration device must accurately deliver the required dose for the product in question in accordance with the approved dosage and the results of such studies must be available.
2. The new device is compatible with the medicinal product.
3. The change must not lead to substantial changes to the product information.
4. The medicinal product can still be delivered accurately.
5. For veterinary medicinal products, the device is not critical to the safety of the person administering the product.
6. The medicinal device is not used as a solvent for the medicinal product.
7. If there is a measuring function, the CE mark must cover the measuring function.

1.1.1.1.104 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate, including description, detailed drawing and material composition of the device and supplier where appropriate, including revised Information of the product as needed.

2. Proof of CE marking and if it has a measuring function, proof of CE marking must also include the 4-digit block number.

3. Data to indicate the accuracy, precision and compatibility of the device.

4. Samples of new device where applicable (see NTA, Sample Requirements in Member States).

5. Reason for deleting the device.

Note: for B.IV.1.c), applicants are reminded that any change resulting in a "new pharmaceutical form" requires the submission of an extension application.

B.IV.2 Change in specification parameters and/or limits of a measuring or administration device for veterinary medicinal products	Conditions that are met	Documentation to be supplied	Type of procedure
a) Tightening the specification limits	1, 2, 3, 4	1, 2	IA
b) Adding a new specification parameter to the specification with the corresponding test method	1, 2, 5	1, 2, 3, 4, 6	IA
c) Extending the limits of the approved specifications, which has a significant effect on the overall quality of the device			II
d) Deletion of a specification parameter that has a significant effect on the overall quality of the device			II
e) Adding a specification parameter as a result of a safety or quality issue		1, 2, 3, 4, 6	IB
f) Deleting an irrelevant specification parameter (e.g. deleting an obsolete parameter)	1, 2	1, 2, 5	IA

1.1.1.1.105 Conditions

1. The change is not a consequence of any commitment from previous assessments to review the specification limits (e.g, made during the marketing authorization application procedure or type II variation procedure) unless the supporting documentation has already been assessed and approved within another procedure.
2. The change should not be the result of unexpected events that arise during production.
3. Any changes must be within the currently approved limits.
4. The testing procedure remains the same
5. Any new test method does not involve a new non-standard technique or a standard technique used in a new way.

1.1.1.1.106 Documentation

1. Amendment of the relevant sections of the file (submitted in EU-CTD format or NTA format volume 6B for veterinary products, as appropriate.
2. Comparison table of current and proposed specifications.
3. Details of each new analytical method and summary of validation data.

4. Batch analysis data on two production batches for all tests in the new specifications.

5. Rationale/risk assessment indicating that the parameter is reasonable or not significant.

6. Justification for new specification parameters and limits

B.IV.3 Change in the testing procedure of a measuring or administration device for veterinary medicinal products	Conditions that are met	Documentation to be supplied	Type of procedure
a) Minor change to an approved test procedure	**1, 2**	**1, 2**	**IA**

b) Other changes to a test process (including replacement or addition)	**1, 3**	**1, 2**	**IA**
c) Deleting a test procedure if an alternative test procedure is already authorized	**4**	**1**	**IA**

1.1.1.1.107 conditions

1. Adequate validation studies have been performed in accordance with relevant guidelines and demonstrate that the updated test procedure is at least equivalent to the previous test procedure.

2. The method of analysis should remain the same.

3. Any new test method does not involve a new non-standard technique or a standard technique used in a new way

4. An alternative test procedure is already authorized for the specification parameters and this procedure has not been added through the IA/IA (IN) notification.

1.1.1.1.108 Documentation

1. Amendment of relevant sections of the file (submitted in EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a description of the analytical methodology and a summary of the validation data.

2. The results of the comparative evaluation or if the results of the justified comparative analysis show that the actual test and the proposal are equivalent. This requirement is not applicable in case of adding a new test procedure.

B.V. CHANGES TO MARKETING AUTHORIZATION RESULTING FROM OTHER REGULATORY PROCEDURES S BVa) *SMP/VAMF*

B.V.a. 1. Inclusion of a new, updated or amended Master Plasma file in the marketing authorization file of a medicinal product. (SMP stage 2 procedure)	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) The first inclusion of a new Master Plasma file that affects the properties of the finished product			**II**
b) The first inclusion of a new Plasma Master file does not affect the properties of the finished product		**1, 2, 3, 4**	**IB**
c) Inclusion of an updated / changed Master Plasma file when changes affect the properties of the finished product		**1, 2, 3, 4**	**IB**

d) Inclusion of an updated / changed Master Plasma file when the changes do not affect the properties of the finished product	**1**	**1, 2, 3, 4**	**IA_{IN}**

1.1.1.1.109 Conditions

1. The updated or amended Master Plasma document has been granted a certificate of conformity with Union legislation in accordance with Annex I of Directive 2001/83/EC.

1.1.1.110 Documentation

1. Statement that the SMP Certificate and Assessment Report are fully applicable to the authorized product, the SMP holder has provided the SMP Certificate, the Assessment Report and the SMP file to the AM (where the MAM is different from the SMP holder), the Certificate The SMP and Evaluation Report supersede the previous SMP documentation for this Marketing Authorization.

2. SMP Certificate and Assessment Report.

3. An expert statement describing all changes introduced with the certified SMP and the assessment of their potential impact on finished products including product-specific risk assessments.

4. The flight application form must clearly describe the "present" and "proposed" EMA SMP certificate (code number) in the MA file. Where applicable, the variation application form must clearly indicate all other SMPs to which the medicinal product refers even if they are not the subject of the application.

B.V.a. 2 Inclusion of a new, updated or amended Vaccine Antigen file in the marketing authorization file of a medicinal product. (2nd VAMF procedure)	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) First inclusion of a new vaccine antigen master file			**II**
b) Inclusion of an updated / changed vaccine antigen master file, when the changes affect the properties of the finished product		**1, 2, 3, 4**	**IB**
c) Inclusion of an updated/changed vaccine antigen master file, when the changes do not affect the properties of the finished product	**1**	**1, 2, 3, 4**	**IA_{IN}**

1.1.1.1.111 Conditions

1. The update or amendment of the Vaccine Antigen Master document has been granted a certificate of conformity with Union legislation in accordance with Annex I of Directive 2001/83/EC.

1.1.1.1.112 Documentation

1. Statement that the VAMF Report and the Assessment Report are fully applicable to the authorized product, the VAMF holder has submitted in the VAMF file, the Assessment Report and the VAMF file to the MAM (where the MAM is different from the VAMF holder) The Evaluation Report replaces the previous VAMF documentation for this Marketing Authorization.

2. VAMF Certificate and Evaluation Report.

3. An expert statement describing all proposed changes with the certified VAMF and assessment of their potential impact on finished products including product specific risk assessments.

4. The change application form must clearly describe 'VAMF EMA Certificate (code number) 'present' and 'proposed' in the MA file. Where applicable, the variation application form must also clearly indicate all other VAMFs to which the medicinal product refers even if they are not the subject of the application.

B.V.b) *Reference*

B.V.b..1 Updating the quality file in order to implement the result of a Union referral procedure	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) The change applies the result of the referral	**1**	**1, 2**	**IA_{IN}**
b) The harmonization of the quality file was not part of the reference and the update aims to harmonize it			**II**

1.1.1.1.113 Conditions

1. The result does not require further evaluation.

1.1.1.1.114 Documentation

1. Attached to the covering letter of the amendment application: A reference to the said Commission's decision.

2. Changes introduced during the referral procedure must be clearly stated in the submission.

C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES

C.I HUMAN AND VETERINARY MEDICINAL PRODUCTS

C.I. 1 Changes to the Summary of Product Characteristics, labeling and leaflet in order to implement the outcome of a Union referral procedure	Conditions that are met	Documentation to be supplied	Type of procedure
a) The medicinal product is covered by the defined scope of the procedure	**1**	**1, 2, 3**	**IA_{IN}**
b) The medicinal product is not covered by the defined scope of the procedure, but the changes apply the result of the procedure and no additional new data is required to be submitted by MAM		**1, 2, 3**	**IB**
c) The medicinal product is not covered by the defined scope of the procedure, but the changes (amendments) apply the result of the procedure with additional new data submitted by MAM		**1, 3**	**II**

1.1.1.1.115 Conditions

1. The variation applies the wording required by the authority and does not require the submission of additional information and/or further evaluation.

1.1.1.1.116 Documentation

1. Attached to the cover letter of the amendment application: a reference to the decision of the Commission in question or to the agreement reached by the CMDh (as the case may be) with the Summary of Product Characteristics, Labeling or Package Leaflet.

2. A statement that the proposed Summary of Product Characteristics, Labeling and Package Leaflet is identical for the relevant sections to that attached to the Commission Decision or the agreement reached by the CMDh (as applicable).

3. Revised product information.

C.I. 2 Changes in the Summary of Product Characteristics, Labeling or Package Leaflets of generic / hybrid / biosimilar products after evaluating the same change for the reference product	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Implementation of changes, for which there are no additional new data, it is necessary to be submitted by MAM		**1, 2**	**IB**
b) Implementation of changes that require to be further substantiated with new additional data to be submitted by MAM (e.g. comparability)			**II**

1.1.1.1.117 Documentation

1. Attached to the change application cover letter: EMA / NCA request, if applicable.

2. Revised product information.

C.I. 3 Changes to the Summary of Product Characteristics, Labeling or Package Leaflet of human medicinal products intended to implement the result of a procedure related to the RPPS or PASS or the result of the assessment made by the competent authority under Article 45 or 46 of Regulation (EC) No. 1901/2006	Conditions that are met	Documentation to be supplied	Type of procedure
a) Application of the wording approved by the competent authority	**1**	**1, 2**	**IA_{IN}**
b) Implementation of changes that require further testing with additional new data to be submitted by MAM		**2**	**II**

1.1.1.1.118 Conditions

1. The variation applies the wording required by the competent authority and does not require the submission of additional information and/or further assessment.

1.1.1.1.119 Documentation

1. Attached to the cover letter of the variation application: reference to the agreement / assessment of the competent authority.

2. Revised product information.

C.I. 4 Changes to the Summary of Product Characteristics, Labeling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	Conditions that are met	Documentation to be supplied	Type of procedure
			II

Note: This change does not apply when new data is submitted under variant C.I.13. In such cases, the change(s) to the SMPC, labeling and/or package insert are covered by the scope of variation C.I.13.

C.I.5 Change in the legal status of a medicinal product for centrally authorized products	Conditions that are met	Documentation to be supplied	Type of procedure

a) For generic / hybrid / biosimilar medicinal products after a change in the approved legal status of the reference medicinal product		**1, 2**	**IB**
b) All other legal changes			**II**

1.1.1.1.120 Documentation

1. Attached to the cover letter of the change application: proof of authorization for the change of legal status (e.g. reference to the decision of the Commission in question).

2. Revised product information.

Note: For Nationally Authorized Products approved with MRP / DCP, the change of legal status must be handled at the national level (not through an MRP variation).

C.I.6 Changes in therapeutic indications	Conditions that are met	Documentation to be supplied	Type of procedure
a) Addition of a new therapeutic indication or modification of an approval			**II on d**
b) Deleting a therapeutic indication			**IB**

*Note:*Where the change occurs in the context of implementing the result of a referral procedure, or - for a generic / hybrid / biosimilar product - when the same change is made for the reference product, variations CI1 and CI2 apply, respectively.

C.I.7 Deletion of:	Conditions that are met	Documentation to be supplied	Type of procedure
a) pharmaceutical form		**1, 2**	**IB**
b) strength		**1, 2**	**IB**

1.1.1.1.121 Documentation

1. Statement that the remaining presentation of the product is suitable for the dosage instructions and duration of treatment as mentioned in the summary of product characteristics.

2. Revised product information

*Note:*In cases where a given pharmaceutical form or strength has received a marketing authorization which is separate from the marketing authorization for other pharmaceutical forms or strengths, the deletion of the former will not be a change, but a withdrawal of the authorization of marketing.

CI8 Presentation of, or changes to, a summary of the pharmacovigilance system for medicinal products for human use(*)	Conditions that are met	Documentation to be supplied	Type of procedure
a) Submission of an overview of the pharmacovigilance system, changes to the QPPV (including contact details) and/or changes to the Pharmacovigilance System Master File (PSMF) location		**1, 2**	**IA_{IN}**

1.1.1.1.122 Documentation

1. Summary of the pharmacovigilance system, or update of relevant elements (as applicable):

— Evidence that the applicant has available a qualified person responsible for pharmacovigilance and a statement signed by the applicant to the effect that the applicant has the necessary means to fulfill the duties and responsibilities listed in Title IX of Directive 2001/83/EC.

— Contact details of the QPPV, the Member States in which the QPPV is located and performs his/her tasks

— PSMF location

2. PSMF number (if available)

Note: This variation covers the entry of a PSMF whether or not the AM technical file contains a PHSF. Once the Article 57 database is operational, changes to the QPPV, including contact details (telephone and fax numbers, postal address and email address) as well as changes to the PSMF location (street, city, postcode , country) will be updated in the Article 57 database only (without the need for an amendment).

When the MAM takes the opportunity to update the above information through the Article 57 database, the MAM must indicate in the marketing authorization that the updated information of those features is included in the database.

(*) For the introduction of a new pharmacovigilance system for veterinary medicinal products please refer to C.II.7.

C.I.9 Changes to an existing pharmacovigilance system as described in the detailed description of the pharmacovigilance system (PHSF).	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
a) Change in QPPV contact details and/or QPPV and/or support procedure	**1**	**1**	**IA_{IN}**
b) Changes in the safety database and / or larger contractual agreements for the fulfillment of pharmacovigilance obligations and / or change of the country subject to pharmacovigilance activities	**1, 2, 3**	**1**	**IA_{IN}**
c) Other changes in the PHSF that do not affect the functioning of the pharmacovigilance system (e.g. change of main storage / archiving location, administrative changes)	**1**	**1**	**IA**
d) Changes to a PHSF after evaluation of the same PHSF in relation to another medicinal product of the same MAM	**4**	**1, 2**	**IA_{IN}**

1.1.1.1.123 Conditions

1. The pharmacovigilance system remains unchanged.
2. The database system is validated (when applicable).
3. Data transfer from other database systems is validated (where applicable).
4. The same changes in the PHSF are presented for all medicinal products of the same MAM (latest PHSF version)

1.1.1.1.124 Documentation

1. The latest version of the PHSF and, where applicable, the latest version of the product-specific appendix. These should include for changes in QPPV a) CV summary of the new QPPV, b) Proof of QPPV EudraVigilance registration, and c) a new MAM and QPPV statement regarding their availability and means of reporting adverse drug reactions signed by the new QPPV and MAM, and reflecting any other

changes, e.g. in the organization chart.

Where the QPPV and/or QPPV contact details are not included in the PHSF or do not exist in a PHSF, submission of the revised version of the PHSF is not required and the application form must be provided.

2. Reference of the application/procedure and product in which the changes have been accepted.

Note: C.I.9 covers changes to an existing pharmacovigilance system 1) for veterinary medicinal products and 2) for human medicinal products that have not yet introduced a PSMF.

Note for a): Once the Article 57 database is operational, changes to the QPPV, including contact details (telephone and fax numbers, postal address and email address) can only be updated through the Article 57 database (without the need for a change). When the User of the Use of the Use of the opportunity to update this information through the database of Article 57, the MAM must indicate in the marketing authorization that the updated information of those features is included in the database.

Note for d): Evaluation of a PHSF submitted as part of a new MAA / Extension / Variation may cause changes at the request of the national competent authority/EMA to this PHSF. When this happens, the same changes can be entered in the PHSF in other marketing authorizations of the same MAM, submitting a Type (Grouped) variation IA_{IN}.

C.I.10 Change in the frequency and / or date of submission of periodic safety update reports (RPPS) for human medicinal products	Conditions that are met	Documentation to be supplied	Type of procedure
	1	**1, 2**	**IA_{IN}**

1.1.1.1.125 Conditions

1. Change in frequency and/or date of submission of RPPS agreed by CHMP/CMDh/NCA

1.1.1.1.126 Documentation

1. Attached to the variation request letter: A reference to the competent authority agreement (in the case of marketing authorizations granted under the centralized procedure, CHMP).

2. The revised frequency and/or submission date of the RPPS (for medicinal products authorized through the centralized procedure, the entirety of the appendices, including the revised Annex II, must be provided).

Note: This change only applies where the RPPS cycle is specified in the marketing authorization by means other than a reference to the Union reference date list and where submission of the RPPS is required.

C.I.11 Submission or amendment of the obligations and conditions of a marketing authorisation, including the risk management plan	Conditions that are met	Documentation to be supplied	Type of procedure
a) Application of the wording approved by the competent authority	**1**	**1, 2**	**IA_{IN}**
b) Implementation of changes (changes) which require to be further supported with new additional data that must be submitted by the User where significant assessment is required by the competent authority(*)			**II**

1.1.1.1.127 Conditions

1. The changes implement the action requested by the authority and do not require the submission of additional information and/or further assessment.

1.1.1.1.128 DOCUMENTATION

1. Attached to the change request letter: A reference to the relevant decision of the competent authority.

2. Updating the relevant section of the file.

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 circumstances and conditional marketing authorization .

(*) The introduction of a risk management plan required by the competent authority always requires significant assessment.

C.I.12 Inclusion or deletion of the black symbol and explanatory statements for medicinal products in the list of medicinal products subject to additional monitoring	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
	1	**1, 2**	**IA_{IN}**

1.1.1.1.129 Conditions

1. The medicinal product is included or removed from the list of medicinal products subject to additional monitoring (as the case may be)

1.1.1.1.130Documentation

1. Attached to the amendment application cover letter: A reference to the list of medicinal products subject to additional monitoring

2. Revised product information

*Note:*This variation covers the situation where the inclusion or deletion of the black symbol and explanatory statements is not done as part of another regulatory procedure (e.g. renewal or change procedures affecting product information).

C.I.13 Other variations not specifically covered elsewhere in this Appendix involving the submission of studies to the competent authority(*)	**Conditions that are met**	**Documentation to be supplied**	**Type of procedure**
			II

*Note:*In cases where the evaluation by the competent authority of the submitted data leads to a change of the Summary of Product Characteristics, Labeling or Package Sheet, the corresponding change in the Summary of Product Characteristics, Labeling or Package Sheet is covered by the change.

The inclusion of the Statementon of Conformity provided for in Article 28 (3) of Regulation (EC) No. 1901/2006 is also covered by this variation (provided that the requirements of Regulation (EC) No. 1901/2006 are met).

(*) This variation does not apply to variations that may be considered Type IB by default under any other section of this Annex.

1.1.1.1.131