APPLICATION FOR VARIATION TO A MARKETING AUTHORISATION

HUMAN ☐ **VETERINARY** ☐

☐ **NATIONAL AUTHORISATION IN MRP** **Variation procedure number(s)[1]: .....**

☐ **EU AUTHORISATION**

☐ **NATIONAL AUTHORISATION**

Reference Member State / Reference Authority for worksharing

☐AT ☐BE ☐BG ☐CY ☐CZ ☐DE ☐DK ☐EE ☐EL ☐ES ☐FI ☐FR ☐HR ☐HU ☐IE
☐IS ☐IT ☐LI ☐LT ☐LU ☐LV ☐MT ☐NL ☐NO ☐PL ☐PT ☐RO ☐SE ☐SI ☐SK
☐UK ☐EMA

Concerned Member State(s)

☐AT ☐BE ☐BG ☐CY ☐CZ ☐DE ☐DK ☐EE ☐EL ☐ES ☐FI ☐FR ☐HR ☐HU ☐IE
☐IS ☐IT ☐LI ☐LT ☐LU ☐LV ☐MT ☐NL ☐NO ☐PL ☐PT ☐RO ☐SE ☐SI ☐SK
☐UK ☐NONE

Type of Application (tick all applicable options)

- ☐ **Type IA_{IN}**
- ☐ **Type IA**
- ☐ **Type IB unforeseen[2]**
- ☐ **Type IB**
- ☐ **Type II**
- ☐ **Type II Art. 29[4]**
- ☐ **Single variation**
- ☐ **Grouping of variations**
  - ☐ **Including a line extension[3]**
- ☐ **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**

[1] Human Medicinal Products: Number to be completed by the Marketing Authorisation Holder, reflecting the correct sequential Mutual Recognition Procedure Number according to Chapter 1 of the 'Best Practice Guides for the submission and processing of variations in the Mutual Recognition Procedure' (http://www.hma.eu).
Veterinary Medicinal Products: Variation number to be issued by the Reference Member State before submission of the application according to the corresponding VMRFG Best Practice Guide (http://www.hma.eu).
Centralised procedure: The sequential EMA procedure number (not the MAH's internal number) should be provided here, when known to the Marketing Authorisation Holder. For worksharing procedures with EMA as reference authority, the 'high-level' EMA worksharing procedure number needs to be provided.
[2] 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.
[3] If the variations are part of a grouped submission including a line-extension, this application form should be considered an annex to the application form for the extension application.
[4] Type II variation submitted under Article 29 of Regulation (EC) No 1901/2006.

Name and address of the Applicant/MA holder[5]:	Name and address of contact person[6]: Telephone number: Fax number (optional): E-mail:

[5] 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.

[6] 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).

PRODUCTS CONCERNED BY THIS APPLICATION[7]

(Invented)Name(s):	Active substance(s)	Pharmaceutical form	Strength	MA holder name(s):	MA number(s):[8]	MRP Variation Number[8]

[7] 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*).
[8] 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

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
☒ a)	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[9,10]	PROPOSED[9,10]
D-U-N-S number:[11] EU or National ASMF number:[12]	D-U-N-S number:[11] EU or National ASMF number:[12]

OTHER APPLICATIONS[13]

[9] Specify the precise present and proposed wording or specification, including dossier section number(s) at the lowest possible level.
[10] For SPC, labelling and package leaflet changes, underline or highlight the changed words presented in the table above or provide as a separate Annex
[11] 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
[12] If applicable, include EU or National ASMF reference number (only if EU ASMF reference number is not available)
[13] Due to complexity it is not necessary to complete this section for worksharing or grouped variations affecting more than one MA.

Type II variations – new indications – orphan medicinal product information:

(For human medicinal products only; delete this section if the variation does not relate to a new indication)

HAS ORPHAN DESIGNATION BEEN APPLIED FOR, FOR THIS NEW INDICATION?

❍ No
❍ Yes Orphan Designation Procedure Number:
- ❍ Pending
- ❍ Orphan Designation granted
  Date (yyyy-mm-dd):
  Based on the criterion of "significant benefit": ❍ Yes ❍ No
  Number in the Community Register of Orphan Medicinal Products:
  ☐ Attach copy of the Designation Decision
- ❍ Orphan Designation Refused
  Date (yyyy-mm-dd):
  Commission Decision Reference Number:
- ❍ Orphan Designation Withdrawn
  Date (yyyy-mm-dd):

INFORMATION RELATING TO ORPHAN MARKET EXCLUSIVITY

Has any medicinal product been designated as an Orphan medicinal product for a condition relating to the new indication proposed in this variation application?

❍ No
❍ Yes
Please specify the EU Orphan Designation Number(s):

If yes, has any of the designated Orphan medicinal product(s) been granted a marketing authorisation in the EU?

❍ No
❍ Yes
Please specify:
- Name, therapeutic indications, strength, pharmaceutical form of the authorised product:
- Name of the marketing authorisation holder:
- Marketing authorisation number(s):
- Date of authorisation:

If yes, is the medicinal product, subject of this application, considered as "similar" to any of the authorised Orphan medicinal product(s)? *(as defined in Article 3 of Commission Regulation (EC) No 847/2000)*
❍ No (module 1.7.1 to be completed)
❍ Yes (modules 1.7.1 and 1.7.2 to be completed)

Note: Repeat as necessary

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[14] 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[15] PIP Decision Number(s):
❍ Product-Specific Waiver[16] Waiver Decision Number(s):
❍ Class waiver Waiver Decision Number(s):

(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

[14] 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")
[15] To be ticked when the PIP Opinion includes a waiver
[16] To be ticked only if there is a product-specific waiver opinion covering all the subsets of the paediatric population

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[17]
- ☐ Labelling
- ☐ Package leaflet
- ☐ Mock-ups[18]
- ☐ Specimens[18]

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 paid;
- ☐ 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[19]: ☐ Next production run/next printing
☐ Date: _____

[17] only for centrally authorised products (Annex II of the EU MA)
[18] 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)

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

Fees paid *(if applicable) Amount*[20]

_____

Please specify fee category under National rules[20] _____

Main Signatory[21]

_____

Print name _____

Status (Job title) _____

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 _____

[20] For submissions to the EMA (incl worksharing procedures which include MRP and/or purely national products), this section can be left blank.
[21] 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**
☒ f)	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**	
☒ z)	Other variation	☐IA ☒IB ☐II	☐ **Art 5**

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**	
☒ z)	Other variation	☐IA ☒IB ☐II	☐ **Art 5**

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

A. Administrative change		Procedure type	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. Date:**

		Procedure type		
☐ **A.1**	**Change in the name and/or address of the marketing authorisation holder**	☐IA_{IN}	☐IB¤	**Implement. Date:**

¤ 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		
☐ a)	for Centrally Authorised products	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐ b)	for Nationally Authorised Products	IB		

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

		Procedure type		
☐ **A.3**	**Change in name of the active substance or of an excipient**	☐IA_{IN}	☐IB¤	**Implement. Date:**

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

		Procedure type		
☐ **A.4**	**Change in the name and/or address of a manufacturer (including where relevant quality control testing sites); or an ASMF holder; or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where 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)**	☐IA	☐IB¤	**Implement. Date:**

¤ 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		
☐ a)	The activities for which the manufacturer/importer is responsible include batch release	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐ b)	The activities for which the manufacturer/importer is responsible do not include batch release	☐IA	☐IB¤	**Implement. Date:**

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

		Procedure type		
☐ **A.6**	**Change in ATC Code / ATC Vet Code**	☐IA	☐IB¤	**Implement. Date:**

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

			Procedure type		
☐	**A.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)***	☐IA	☐IB¤	**Implement. Date:**

¤ 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	
☐	**A.8**	**Changes to date of the audit to verify GMP compliance of the manufacturer of the active substance***	☐IA	**Implement. Date:**

B.I.a Change in manufacture of the active substance		Procedure type	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. Date:**

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		
☐ a)	The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer.	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐ b)	Introduction of a manufacturer of the active substance supported by an ASMF	II		
☐ c)	The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability	II		
☐ d)	New manufacturer of material for which an assessment is required of viral safety and/or TSE risk	II		
☐ e)	The change relates to a biological active substance or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product	II		
☐ f)	Changes to quality control testing arrangements for the active substance-replacement or addition of a site where batch control/testing takes place	☐IA	☐IB¤	**Implement. Date:**
☐ g)	Introduction of a new manufacturer of the active substance that is not supported by an ASMF and requires significant update to the relevant active substance section of the dossier	II		
☐ h)	Addition of an alternative sterilisation site for the active substance using a Ph.Eur. method	IB		
☐ i)	Introduction of a new site of micronisation	☐IA	☐IB¤	
☐ j)	Changes to quality control testing arrangements for a biological active substance: replacement or addition of a site where batch control/testing including a biological / immunological / immunochemical method takes place	II		
☐ k)	New storage site of Master Cell Bank and/or Working Cell Banks	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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		
☐ a)	Minor change in the manufacturing process of the active substance	☐IA	☐IB¤	**Implement. Date:**
☐ b)	Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product.	II		
☐ c)	The change refers to a biological / immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological substance, which may have a significant impact on the quality, safety and efficacy of the medicinal product and is not related to a	II		

	protocol			
☐ d)	The change relates to a herbal medicinal product and there is a change to any of the following: geographical source, manufacturing route or production	II		
☐ e)	Minor change to the restricted part of an Active Substance Master File	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. Date:**

¤ 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**		
☐ a)	Up to 10-fold increase compared to the originally approved batch size	☐IA	☐IB¤	**Implement. Date:**
☐ b)	Downscaling down to 10-fold	☐IA	☐IB¤	**Implement. Date:**
☐ c)	The change requires assessment of the comparability of a biological/immunological active substance	II		
☐ d)	More than 10-fold increase compared to the originally approved batch size	IB		
☐ e)	The scale for a biological/immunological active substance is increased / decreased without process change (e.g. duplication of line)	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. Date:**

¤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**		
☐ a)	Tightening of in-process limits	☐IA	☐IB¤	**Implement. Date:**
☐ b)	Addition of a new in-process test and limits	☐IA	☐IB¤	**Implement. Date:**
☐ c)	Deletion of a non-significant in-process test	☐IA	☐IB¤	**Implement. Date:**
☐ d)	Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the active substance	II		
☐ e)	Deletion of an in-process test which may have a significant effect on the overall quality of the active substance	II		
☐ f)	Addition or replacement of an in-process test as a result of a safety or quality issue	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. Date:**

¤ 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**
☐ a)	Replacement of the strain(s) in a seasonal, pre-pandemic or a pandemic vaccine against human influenza	II

B.I.b Change in control of the active substance		Procedure type	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5** **Implement. Date:**

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		
☐ a)	Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐ b)	Tightening of specification limits	☐IA	☐IB¤	**Implement. Date:**
☐ c)	Addition of a new specification parameter to the specification with its corresponding test method	☐IA	☐IB¤	**Implement. Date:**
☐ d)	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	☐IA	☐IB¤	**Implement. Date:**
☐ e)	Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product	II		
☐ f)	Change outside the approved specifications limits range for the active substance	II		
☐ g)	Widening of the approved specifications limits for starting materials/intermediates, which may have a significant effect on the overall quality of the active substance and/or the finished product	II		
☐ h)	Addition or replacement (excluding biological or immunological substance) of a specification parameter with its corresponding test method as a result of a safety or quality issue	IB		
☐ i)	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		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. Date:**

¤ 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		
☐ a)	Minor changes to an approved test procedure	☐IA	☐IB¤	**Implement. Date:**
☐ b)	Deletion of a test procedure for the active substance or a starting material/reagent/ intermediate, if an alternative test procedure is already authorised.	☐IA	☐IB¤	**Implement. Date:**
☐ c)	Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance	☐IA	☐IB¤	**Implement. Date:**
☐ d)	Substantial change to or replacement of a biological/ immunological/ immunochemical test method or a method using a biological reagent for a biological active substance	II		
☐ e)	Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate	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	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. Date:**

B.I.c.1 Change in immediate packaging of the active substance		Procedure type		
☐ a)	Qualitative and/or quantitative composition	☐IA	☐IB¤	**Implement. Date:**
☐ b)	Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances	II		
☐ c)	Liquid active substances (non sterile)	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤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		
☐ a)	Tightening of specification limits	☐IA	☐IB¤	**Implement. Date:**
☐ b)	Addition of a new specification parameter to the specification with its corresponding test method	☐IA	☐IB¤	**Implement. Date:**
☐ c)	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	☐IA	☐IB¤	**Implement. Date:**
☐ d)	Addition or replacement of a specification parameter as a result of a safety or quality issue	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤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		
☐ a)	Minor changes to an approved test procedure	☐IA	☐IB¤	**Implement. Date:**
☐ b)	Other changes to a test procedure (including replacement or addition)	☐IA	☐IB¤	**Implement. Date:**
☐ c)	Deletion of a test procedure if an alternative test procedure is already authorised	☐IA	☐IB¤	**Implement. Date:**

¤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		
a)	Re-test period/storage period				
☐	1.	Reduction	☐IA	☐IB¤	**Implement. Date:**
☐	2.	Extension of the retest period based on extrapolation of stability data not in accordance with ICH/VICH guidelines*	II		
☐	3.	Extension of storage period of a biological/ immunological active substance not in accordance with an approved stability protocol	II		
☐	4.	Extension or introduction of a re-test period/storage period supported by real time data	IB		
b)	Storage conditions				
☐	1.	Change to more restrictive storage conditions of the active substance	☐IA	☐IB¤	**Implement. Date:**
☐	2.	Change in storage conditions of biological/ immunological active substances, when the stability studies have not been performed in accordance with a currently approved stability protocol	II		
☐	3.	Change in storage conditions of the active substance	IB		
c)	Change to an approved stability protocol		☐IA	☐IB¤	
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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
☐	a)	One unit operation in the manufacturing process of the active substance including the resulting in-process controls and/or test procedures	II
☐	b)	Test procedures for starting materials/reagents/ intermediates and/or the active substance	II

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

	B.I.e.3 Deletion of an approved change management protocol related to the active substance	Procedure type		Implement. Date:
☐		☐IA_{IN}	☐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	
☐	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	IB	
☐	z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. Date:**

B.I.e.5 Implementation of changes foreseen in an approved change management protocol			Procedure type		
☐	a)	The implementation of the change requires no further supportive data	☐IA_{IN}	☐IB¤	
☐	b)	The implementation of the change requires further supportive data	IB		
☐	c)	Implementation of a change for a biological/immunological medicinal product	IB		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

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

B.II.a Change in description and composition of the Finished Product			Procedure type		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

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		
☐	a)	Changes in imprints, bossing or other markings	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	b)	Changes in scoring/break lines intended to divide into equal doses	IB		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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		
☐	a)	Immediate release tablets, capsules, suppositories and pessaries	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	b)	Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses	IB		
☐	c)	Addition of a new kit for a radiopharmaceutical preparation with another fill volume	II		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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		
	a)	Changes in components of the flavouring or colouring system			
☐	1.	Addition , deletion or replacement	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	2.	Increase or reduction	☐IA	☐IB¤	**Implement. Date:**
☐	3.	Biological veterinary medicinal products for oral use for which the colouring or flavouring agent is important for the uptake by target animal species	II		
	b)	Other excipients			
☐	1.	Any minor adjustment of the quantitative composition of the finished product with respect to excipients	☐IA	☐IB¤	**Implement. Date:**
☐	2.	Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product	II		
☐	3.	Change that relates to a biological/immunological product	II		
☐	4.	Any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk	II		
☐	5.	Change that is supported by a bioequivalence study	II		
☐	6.	Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level	IB		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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		
☐ a)	Solid oral pharmaceutical forms	☐IA	☐IB¤	**Implement. Date:**
☐ b)	Gastro-resistant, modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism	II		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. Date:**

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		
☐ a)	Secondary packaging site	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐ b)	Primary packaging site	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐ c)	Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/ immunological medicinal products or for pharmaceutical forms manufactured by complex manufacturing processes	II		
☐ d)	Site which requires an initial or product specific inspection	II		
☐ e)	Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products	IB		
☐ f)	Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for steri medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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		
☐	a)	Replacement or addition of a site where batch control/testing takes place	☐IA	☐IB¤	**Implement. Date:**
☐	b)	Replacement or addition of a site where batch control/testing takes place for a biological/immunological product and any of the test methods performed at the site is a biological/immunological method	II		
	c)	Replacement or addition of a manufacturer responsible for importation and/or batch release			
☐	1.	Not including batch control/testing	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	2.	Including batch control/testing	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	3.	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		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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		
☐	a)	Minor change in the manufacturing process	☐IA	☐IB¤	**Implement. Date:**
☐	b)	Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	II		

☐ c)	The product is a biological/immunological medicinal product and the change requires an assessment of comparability	II	
☐ d)	Introduction of a non-standard terminal sterilisation method	II	
☐ e)	Introduction or increase in the overage that is used for the active substance	II	
☐ f)	Minor change in the manufacturing process of an aqueous oral suspension	IB	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. Date:**

¤ 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**		
☐ a)	Up to 10-fold compared to the originally approved batch size	☐IA	☐IB¤	**Implement. Date:**
☐ b)	Downscaling down to 10-fold	☐IA	☐IB¤	**Implement. Date:**
☐ c)	The change requires assessment of the comparability of a biological/immunological medicinal product or the change in batch size requires a new bioequivalence study	II		
☐ d)	The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes	II		
☐ e)	More than 10-fold increase compared to the originally approved batch size for immediate release (oral) pharmaceutical forms	IB		
☐ f)	The scale for a biological/immunological medicinal product is increased / decreased without process change (e.g. duplication of line)	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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**		
☐ a)	Tightening of in-process limits	☐IA	☐IB¤	**Implement. Date:**
☐ b)	Addition of a new test(s) and limits	☐IA	☐IB¤	**Implement. Date:**
☐ c)	Deletion of a non-significant in-process test	☐IA	☐IB¤	**Implement. Date:**
☐ d)	Deletion of an in-process test which may have a significant effect on the overall quality of the finished product	II		
☐ e)	Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product	II		
☐ f)	Addition or replacement of an in-process test as a result of a safety or quality issue	IB		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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	
☐	z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5** **Implement. Date:**

B.II.c.1 Change in the specification parameters and/or limits of an excipient			Procedure type		
☐	a)	Tightening of specification limits	☐IA	☐IB¤	**Implement. Date:**
☐	b)	Addition of a new specification parameter to the specification with its corresponding test method	☐IA	☐IB¤	**Implement. Date:**
☐	c)	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	☐IA	☐IB¤	**Implement. Date:**
☐	d)	Change outside the approved specifications limits range	II		
	e)	Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	II		
☐	f)	Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method, as a result of a safety or quality issue	IB		
☐	g)	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		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. Date:**

¤ 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		
☐	a)	Minor changes to an approved test procedure	☐IA	☐IB¤	**Implement. Date:**
☐	b)	Deletion of a test procedure if an alternative test procedure is already authorised	☐IA	☐IB¤	**Implement. Date:**
☐	c)	Substantial change to or replacement of a biological/ immunological/ immunochemical test method or a method using a biological reagent	II		
☐	d)	Other changes to a test procedure (including replacement or addition)	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		
	a)	From TSE risk material to vegetable or synthetic origin			
☐		1. For excipients or reagents not used in the manufacture of a biological / immunological active substance or in a biological / immunological medicinal product	☐IA	☐IB¤	**Implement. Date:**
☐		2. For excipients or reagents used in the manufacture of a biological / immunological active substance or in a biological / immunological medicinal product	IB		
☐	b)	Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by a TSE certificate of suitability	II		

¤ 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**		
☐ a)	Minor change in synthesis or recovery of a non-pharmacopoeial excipient or a novel excipient	☐IA	☐IB¤	**Implement. Date:**
☐ b)	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		
☐ c)	The excipient is a biological/immunological substance	II		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. Date:**

B.II.d.1 Change in the specification parameters and/or limits of the finished product		Procedure type		
☐ a)	Tightening of specification limits	☐IA	☐IB¤	**Implement. Date:**
☐ b)	Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐ c)	Addition of a new specification parameter to the specification with its corresponding test method	☐IA	☐IB¤	**Implement. Date:**
☐ d)	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)	☐IA	☐IB¤	**Implement. Date:**
☐ e)	Change outside the approved specifications limits range	II		
☐ f)	Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	II		
☐ g)	Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method as a result of a safety or quality issue	IB		
☐ h)	Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur for the finished product*	☐IA_{IN}	☐IB¤	
☐ i)	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)	☐IA	☐IB¤	
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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		
☐ a)	Minor changes to an approved test procedure	☐IA	☐IB¤	**Implement. Date:**
☐ b)	Deletion of a test procedure if an alternative method is already authorised	☐IA	☐IB¤	**Implement. Date:**
☐ c)	Substantial change to, or replacement of, a biological/ immunological/ immunochemical test method or a method using a biological reagent or replacement of a biological reference preparation not covered by an approved protocol	II		
☐ d)	Other changes to a test procedure (including replacement or addition)	IB		
☐ e)	Update of the test procedure to comply with the updated general monograph in the Ph. Eur.	☐IA	☐IB¤	
☐ f)	To reflect compliance with the Ph.Eur. and remove reference to the outdated internal test method and test method number*	☐IA	☐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		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

B.II.e.1 Change in immediate packaging of the finished product			Procedure type		
	a)	Qualitative and quantitative composition			
☐	1.	Solid pharmaceutical forms	☐ IA	☐IB¤	**Implement. Date:**
☐	2.	Semi-solid and non-sterile liquid pharmaceutical forms	IB		
☐	3.	Sterile medicinal products and biological/ immunological medicinal products.	II		
☐	4.	The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.	II		
	b)	Change in type of container or addition of a new container			
☐	1.	Solid, semi-solid and non-sterile liquid pharmaceutical forms	IB		
☐	2.	Sterile medicinal products and biological/ immunological medicinal products	II		
☐	3.	Deletion of an immediate packaging container that does not lead to the complete deletion of a strength or pharmaceutical form	☐IA	☐IB¤	
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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		
☐	a)	Tightening of specification limits	☐IA	☐IB¤	**Implement. Date:**
☐	b)	Addition of a new specification parameter to the specification with its corresponding test method	☐IA	☐IB¤	**Implement. Date:**
☐	c)	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	☐IA	☐IB¤	**Implement. Date:**
☐	d)	Addition or replacement of a specification parameter as a result of a safety or quality issue	IB		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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		
☐	a)	Minor changes to an approved test procedure	☐IA	☐IB¤	**Implement. Date:**
☐	b)	Other changes to a test procedure (including replacement or addition)	☐IA	☐IB¤	**Implement. Date:**
☐	c)	Deletion of a test procedure if an alternative test procedure is already authorised	☐IA	☐IB¤	**Implement. Date:**

¤ 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		
☐	a)	Non-sterile medicinal products	☐IA	☐IB¤	**Implement. Date:**
☐	b)	The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product	II		
☐	c)	Sterile medicinal products	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		
	a)	Change in the number of units (e.g. tablets, ampoules, etc.) in a pack			
☐	1.	Change within the range of the currently approved pack sizes	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	2.	Change outside the range of the currently approved pack sizes	IB		
☐	b)	Deletion of pack size(s)	☐IA	☐IB¤	**Implement. Date:**
☐	c)	Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/ immunological medicinal products.	II		
☐	d)	Change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) products	IB		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. Date:**

¤ 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		
☐	a)	Change that affects the product information	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	b)	Change that does not affect the product information	☐IA	☐IB¤	**Implement. Date:**

¤ 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		
☐	a)	Deletion of a supplier	☐IA	☐IB¤	**Implement. Date:**
☐	b)	Replacement or addition of a supplier	☐IA	☐IB¤	**Implement. Date:**
☐	c)	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		
	a)	Reduction of the shelf life of the finished product			
☐	1.	As packaged for sale	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	2.	After first opening	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	3.	After dilution or reconstitution	☐IA_{IN}	☐IB¤	**Implement. Date:**
	b)	Extension of the shelf life of the finished product			
☐	1.	As packaged for sale (supported by real time data)	IB		
☐	2.	After first opening (supported by real time data)	IB		
☐	3.	After dilution or reconstitution (supported by real time data)	IB		
☐	4.	Extension of the shelf-life based on extrapolation of stability data not in accordance with ICH/VICH guidelines*	II		
☐	5.	Extension of the shelf-life of a biological/ immunological medicinal product in accordance with an approved stability protocol.	IB		
☐	c)	Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	II		
☐	d)	Change in storage conditions of the finished product or the diluted/reconstituted product	IB		
☐	e)	Change to an approved stability protocol	☐IA	☐IB¤	
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. Date:**

¤ 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
☐	a)	One or more unit operations in the manufacturing process of the finished product including the resulting in-process controls and/or test procedures	II
☐	b)	Test procedures for excipients / intermediates and/or the finished product.	II

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

	B.II.g.3 Deletion of an approved change management protocol related to the finished product	Procedure type		
☐		☐IA_{IN}	☐IB¤	**Implement. Date:**

¤ 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	
☐	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	IB	
☐	z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5** **Implement. Date:**

B.II.g.5 Implementation of changes foreseen in an approved change management protocol			Procedure type		
☐	a)	The implementation of the change requires no further supportive data	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	b)	The implementation of the change requires further supportive data	IB		
☐	c)	Implementation of a change for a biological/immunological medicinal product	IB		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. Date:**

¤ 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
☐	a)	Studies related to manufacturing steps investigated for the first time for one or more adventitious agents	II
☐	b)	Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier	
		1) with modification of risk assessment	II
		2) without modification of risk assessment	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**		
	a)	European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.			
☐	1.	New certificate from an already approved manufacturer	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	2.	Updated certificate from an already approved manufacturer	☐IA	☐IB¤	**Implement. Date:**
☐	3.	New certificate from a new manufacturer (replacement or addition)	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	4.	Deletion of certificates (in case multiple certificates exist per material)	☐IA	☐IB¤	
☐	5.	New certificate for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free	IB		
	b)	European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient			
☐	1.	New certificate for an active substance from a new or an already approved manufacturer	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	2.	New certificate for a starting material/reagent/ intermediate/or excipient from a new or an already approved manufacturer	☐IA	☐IB¤	**Implement. Date:**
☐	3.	Updated certificate from an already approved manufacturer	☐IA	☐IB¤	**Implement. Date:**
☐	4.	Deletion of certificates (in case multiple certificates exist per material)	☐IA	☐IB¤	
☐	5.	New/updated certificate from an already-approved/new manufacturer using materials of human or animal origin for which an assessment of the risk with respect to potential contamination with adventitious agents is required	II		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. Date:**

¤ 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**		
	a)	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			
☐	1.	Active substance	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	2.	Excipient/active substance starting material	☐IA	☐IB¤	**Implement. Date:**
☐	b)	Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	☐IA	☐IB¤	**Implement. Date:**
☐	c)	Change in specifications from a national pharmacopoeia of a Member State to the Ph. Eur.	☐IA	☐IB¤	**Implement. Date:**
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5** **Implement. Date:**

¤ 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	
☐	z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. Date:**

B.IV.1 Change of a measuring or administration device			Procedure type		
	a)	Addition or replacement of a device which is not an integrated part of the primary packaging			
☐	1.	Device with CE marking	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	2.	Device without CE marking (for veterinary products only)	IB		
☐	3.	Spacer device for metered dose inhalers or other device which may have a significant impact on the delivery of the active substance in the product (e.g. nebuliser)	II		
☐	b)	Deletion of a device	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	c)	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		
☐	a)	Tightening of specification limits	☐IA	☐IB¤	**Implement. Date:**
☐	b)	Addition of a new specification parameter to the specification with its corresponding test method	☐IA	☐IB¤	**Implement. Date:**
☐	c)	Widening of the approved specifications limits, 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)	Addition of a specification parameter as a result of a safety or quality issue	IB		
☐	f)	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	☐IA	☐IB¤	**Implement. Date:**
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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		
☐	a)	Minor change to an approved test procedure	☐IA	☐IB¤	**Implement. Date:**
☐	b)	Other changes to a test procedure (including replacement or addition)	☐IA	☐IB¤	**Implement. Date:**
☐	c)	Deletion of a test procedure if an alternative test procedure is already authorised	☐IA	☐IB¤	**Implement. Date:**

¤ 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		
☐ a)	First-time inclusion of a new Plasma Master File affecting the properties of the finished product	II		
☐ b)	First-time inclusion of a new Plasma Master File not affecting the properties of the finished product	IB		
☐ c)	Inclusion of an updated/amended Plasma Master File when changes affect the properties of the finished product	IB		
☐ d)	Inclusion of an updated/amended Plasma Master File when changes do not affect the properties of the finished product	☐IA_{IN}	☐IB¤	**Implement. Date:**

¤ 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		
☐ a)	First-time inclusion of a new Vaccine Antigen Master File	II		
☐ b)	Inclusion of an updated/amended Vaccine Antigen Master File, when changes affect the properties of the finished product	IB		
☐ c)	Inclusion of an updated/amended Vaccine Antigen Master File, when changes do not affect the properties of the finished product	☐IA_{IN}	☐IB¤	**Implement. Date:**

¤ 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		
☐ a)	The change implements the outcome of the referral*	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐ b)	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	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. Date:**

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		
☐ a)	The medicinal product is covered by the defined scope of the procedure	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐ b)	The medicinal product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure and no new additional data is required to be submitted by the MAH	IB		
☐ c)	The medicinal product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure with new additional data submitted by the MAH	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
☐ a)	Implementation of change(s) for which no new additional data is required to be submitted by the MAH	IB
☐ b)	Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH (e.g. comparability)	II

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		
☐ a)	Implementation of wording agreed by the competent authority	☐IA_{IN}	☐IB¤	
☐ b)	Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH	II		
☐ z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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

☐	a)	For generic/hybrid/biosimilar medicinal products following an approved legal status change of the reference medicinal product	IB
☐	b)	All other legal status changes	II

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

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

C.I.8 Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use*			**Procedure type**	
☐	a)	Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	☐IA_{IN}	☐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**		
☐	a)	Change in the QPPV and/or QPPV contact details and/or back-up procedure	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	b)	Change(s) in the safety database and/or major contractual arrangements for the fulfilment of pharmacovigilance obligations, and /or change of the site undergoing pharmacovigilance activities	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	c)	Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system (e.g. change of the major storage/archiving location, administrative changes	☐IA	☐IB¤	**Implement. Date:**
☐	d)	Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	☐IA_{IN}	☐IB¤	**Implement. Date:**
☐	z)	Other variation	☐IA ☐IB ☐II		☐ **Art 5 Implement. Date:**

¤ 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**	☐IA_{IN}	☐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**		
☐	a)	Implementation of wording agreed by the competent authority	☐IA_{IN}	☐IB¤	**Implement. Date:**

☐	b)	Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the competent authority is required*	II	
☐	z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. Date:**

¤ 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**	☐IA_{IN}	☐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	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. Date:**

	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
☐ a)	Deletion as a result of a safety issue	II
☐ b)	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
☐ a)	Which has not been assessed by the relevant national competent authority/EMA for another product of the same MAH	II
☐ b)	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)**	☐IA_{IN}	☐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	
☐ z) Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. Date:**

	Procedure type		
☐ **D.1 Change in the name and/or address of the VAMF certificate holder**	☐IA_{IN}	☐IB¤	**Implement. Date:**

¤ 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**	☐IA_{IN}	☐IB¤	**Implement. Date:**

¤ 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-**	☐IA_{IN}	☐IB¤	**Implement. Date:**

¤ 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**	☐IA	☐IB¤	**Implement. Date:**

¤ 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**	☐IA	☐IB¤	**Implement. Date:**

¤ 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**	☐IA	☐IB¤	**Implement. Date:**

¤ 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**	☐IA	☐IB¤	**Implement. Date:**

¤ 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**	☐IA	☐IB¤	**Implement. Date:**

¤ 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**		
☐ a)	The new test kit has not previously been approved in the PMF for any blood centre for testing of donations	II		
☐ b)	The new test kit has been approved in the PMF for other blood centre(s) for testing of donations	☐IA	☐IB¤	**Implement. Date:**

¤ 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.**	☐IA	☐IB¤	**Implement. Date:**

¤ 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**		
☐ a)	The new blood containers are CE-marked	☐IA	☐IB¤	**Implement. Date:**
☐ b)	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**		
☐ a)	storage and/or transport conditions	☐IA	☐IB¤	**Implement. Date:**
☐ b)	maximum storage time for the plasma	☐IA	☐IB¤	**Implement. Date:**

¤ 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