DECISION
No. 4/23.03.2010

on approval of Norms of the National Medicines Agency administrative procedure for the handling of variations

The Scientific Council of the National Medicines Agency, set up based on Order of the Minister of Public Health No. 1027/22.05.2008, reunited on summons of the National Medicines Agency President in the ordinary meeting of 23.03.2010 in accord with Article 10 of Government Ordinance No. 125/1998 related to the set up, organisation and operation of the National Medicines Agency, approved as amended through Law No. 594/2002, as amended, agrees on the following

DECISION

Art. 1. – The Norms of the National Medicines Agency administrative procedure for the handling of variations is approved, in accordance with the Annex which is integral part of this Decision.

Art. 2. – On the day of the coming into force of this Decision, NMA Scientific Council Decision No. 22/22.05.2006, approved through Minister of Health Order No. 874/17.07.2006 on approval of Norms of the National Medicines Agency administrative procedure for the handling of variations is repealed.

Art. 3. – This decision is approved through Minister of Health Order and is published in the Official Gazette of Romania, Part I.

PRESIDENT
of the Scientific Council
of the National Medicines Agency,

Acad. Prof. Dr. Victor Voicu

ANNEX

NORMS

of the National Agency for Medicines and Medical Devices administrative procedure for the handling of variations

CHAPTER I
Introduction

Art. 1. - These norms establish the National Agency for Medicines and Medical Devices' (hereinafter NAMMD) administrative procedure for the handling of variations to the terms of Marketing Authorisation of medicinal products for human use authorised by national procedure, including simplified procedures of the Collaboration Agreement of Drug Regulatory Authorities in European Union Associated Countries (CADREAC)/*New Collaboration Agreement between Drug Regulatory Authorities in Central and Eastern European Countries* (nCADREAC).

The definitions mentioned in Law No. 95/2006 on healthcare reform, as amended, title XVII – The medicinal product, as well as those included in Regulation (EC) No. 1234/2008 of the Commission Regulation (EC) of 24 November 2008, concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, hereinafter 'The variations regulation'.

Art. 3. – In accordance with these norms, the terms '*variation'* and 'change' mentioned under Art. 2 (1) of the Regulation concerning variations are synonyms.

Art. 4. – In accordance with the present norms, the applicants belonging to the same parent company or to the same group of societies, as well as the applicants who have signed agreements or adopted concerted practices referring to the medicinal products concerned should be considered as one and the same marketing authorisation holder.

Art. 5. – The assessment of the application(s) for variation is performed in accordance with the Guideline for the enforcement of the procedures mentioned in Chapters II, III and IV of the Commission Regulation (EC) No 1234/2008 of 24 November 2008, concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (2009/C 323/04) and of the Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (2010/C 17/01), hereinafter the *Commission Classification Guideline*, in Notice to applicants, volume 2C.

CHAPTER II

Scope

Art. 6. - These Norms apply to the applications concerning Type IA, IB minor variations and Type II major variations to the terms of Marketing Authorisation.

Art. 7. - These Norms do not apply to notifications for line extension(s) of Marketing Authorisations and transfers of a Marketing Authorisation.

CHAPTER III
Classification of variations

Art. 8. – The classification mentioned under Art. 3 of the Variations Regulation is enforced, in relation to any variation proposed.

Art. 9. - In case a variation leads to the revision of the Summary of Product Characteristics/labelling/attached leaflet, this revision is considered as part of the respective variation.

CHAPTER IV
Grouping of variations

Art. 10. - The Marketing Authorisation Holder, hereinafter referred to as *the Holder*, shall submit to the NAMMD a notification for variation to terms of Marketing Authorisation according to the Form (the Annex which is integral part of these norms) accompanied by the support documentation and by the fee form issued in accordance with the NAMMD rules in force regarding the submission of the notifications for variation to Marketing Authorisation terms and cashing of corresponding fees.

Art. 11. - The application for variation to the marketing authorisation should contain the elements mentioned in Annex IV to the Variations regulation, submitted in accordance with the titles and numbering of the Rules governing medicinal products in the European Union, volume 2B, Notice to applicants (EU - CTD).

Art. 12. - A notification shall only concern one type IA, IB or II variation.

Art. 13. - (1) The holder may combine several variations within the same application, provided that the respective application corresponds to one of the cases mentioned in Annex III to the Variations Regulation or if joint agreement has been reached previously, namely:

a) minor variations of type IA to the terms of one or several marketing authorisations of the same holder;

b) several variations to the terms of the same marketing authorisation or to one/several variation(s) to the marketing authorisations of the same holder.

(2) In this case, a single application for a Type IA variation shall be submitted for a group containing only Type IA variations, a single application for

a Type IB variation for a group of variations containing at least one Type IB variation, while the others are Type IB or IA, or a single application for a Type II variation for a group containing at least one Type II variation.

(3) Under (1), “marketing authorisation" refers to "global authorisation", as mentioned under Art. 700 (3) of Law No. 95/2006, as amended.

Art. 14. - (1) The MAH informs the NAMMD about their intention to submit a group of variations for the same marketing authorisation at least 60 days prior to submission in view of receiving permission related to the classification of variations which do not meet the requirements mentioned in Annex III to the Variations regulation.

(2) For this purpose, a cover letter shall be forwarded, containing a list of the variations to be classified, in accordance with Art. 3 of the Variations regulation, a brief description of the object of each variation and the justification of the proposal for classification.

(3) The holder is informed in writing about the approval/refusal of the proposal for classification of variations.

(4) In case of refusal, the NAMMD is usually not required to justify their solution.

Art. 15. – In case of type IA variations not requiring immediate notification, the annual reporting system is accepted. In this case, the provisions to Art. 11, 12 and 13 are applicable for the applications for variation.

Art. 16. - (1) Applications for authorisation are not submitted for medicinal products undergoing an authorisation procedure.

(2) As regards the authorisation procedure, additional documents are submitted based on a letter for supplementation of the documentation undergoing an authorisation procedure.

(3) As regards the renewal procedure, it is preferable to submit the application(s) for authorisation at least 6 months prior to the submission of application for authorisation renewal, so that any supplementations required as determined during the procedure related to assessment of the application for renewal, shall be submitted after the end of the procedure, as a variation.

Art. 17. – In view of planning NAMMD resources, the Marketing Authorisation Holder periodically informs the NAMMD about the variations taken into account in 6-12-month time frames.

Art. 18. – In case of applications for grouped variations, the fee is calculated by specific fee for each individual variation, as well as for the variation defining the group (in case of several marketing authorisations for each authorisation of the group affected by the variation), and for each variation of the respective group, other than the one defining the group.

Art. 19. – Invalidation or request for reclassification of variation does not imply retention of the assessment fee; this shall be available to the holder for payment of certain further services.

Art. 20. – When applicable, the NAMMD proceeds to fee reconciliation of the variations to the marketing authorisation terms.

CHAPTER V
Administrative procedure for the handling of Type IA variations to the terms of the Marketing Authorisation

Art. 21. – In Case of a Type IA variation, the holder submits to the NAMMD an application containing the elements mentioned in Annex IV to the Variations Regulation. The application is submitted within 12 months as of the enforcement of the change.

Art. 22. – The application should be submitted right after the enforcement of the change of the variations requiring immediate approval for a continuous surveillance of the respective medicinal product.

Art. 23. – The requirements which must be met so that a change may be subject to a Type IA variation application and to Type IA variations which must be notified to the NAMMD immediately following enforcement are accurately listed in the Commission Classification Guideline.

Art. 24. – The application for variation to the marketing authorisation should include:

a) a cover letter;

b) the fee form of the assessment fee;

c) proof of discharge to the NAMMD (copy of the document for fee encashment, containing the identification data of the variation subject to payment);

d) a filled-in application for variation form, including the details of the concerned marketing authorisation(s), as well as a description of all required changes, while stating the date of their enforcement. If a variation represents a consequence to another, or if it is correlated with another, a description of the relationship between these changes should be provided in the appropriate section of the application form, if applicable;

e) a reference to the section in the Commission Classification Guideline or a reference to the recommendation published in accordance with Art. 5 of the Variations Regulation, used for the respective request, if needed;

f) all documents stated in the Commission Classification Guideline, including the letters for approval of variations in the EU or other EU Member States, if needed;

g) in case the changes affect the Summary of Product Characteristics, the labelling or the leaflet: the revised Summary of Product Characteristics, labelling or leaflet (hereinafter called *product information*), presented in the adequate format. In case the design and readability of the secondary and primary packages or of the leaflet are affected by a Type IA change, drafts and samples should be

provided in accordance with Notice to Applicants, volume 2A, Chapter 7, or in accordance with the discussions with the NAMMD, on a case-by-case basis.

Art. 25. – For Type IA variations concerning several marketing authorisations of the same holder, grouped in accordance with Art. 7 of the Variations Regulation, a joint application form and cover letter should be simultaneously submitted, together with the support documentation and with the revised product information (if needed), for each medicinal product considered.

Art. 26. – At least 15 days prior to the submission of the documents indicated under Art. 24 c) - g), the holder submits to the NAMMD a cover letter and a filled-in fee form.

Art. 27. – Within 30 days from the application submission, the holder is informed in writing by the NAMMD about the approval/refusal of the variation and the grounds for refusal, if any.

Art. 28. – The lack of documents in the application for variation does not result in variation refusal if the holder provides the missing documents on NAMMD request within 15 days as of application receipt.

Art. 29. – In case of grouped Type IA variations, the NAMMD clearly informs the holder about the approval/refusal of each variation included in the group.

Art. 30. – In case of NAMMD refusal of a type IA variation, the holder stops application of the change immediately after receipt of the notice.

Art. 31. – In case the marketing authorisation requires changes, this is updated by the NAMMD within 60 days as of the communication of the acceptance of the variation, for type IA changes not requiring immediate notification, and within 6 months, for type IA changes requiring immediate notification for ongoing surveillance of the concerned medicinal product.

CHAPTER VI
Administrative procedure for the handling type IB variations to marketing authorisation terms

Art. 32. - In case of a Type IB variation, prior to the enforcement of the change, the holder submits to the NAMMD an application containing the elements mentioned in Annex IV to the Variations Regulation.

Art. 33. – The Regulation on the Commission Classification Guideline provides examples of Type IB variations.

Art. 34. – The application for variation brought to the marketing authorisation should contain:

a) a cover letter;

b) assessment fee payment form;

c) proof of discharge to the NAMMD (copy of the document for fee encashment, containing the identification data of the variation subject to payment);

d) a filled-in application for variation form, including the details of the concerned marketing authorisation(s), as well as a description of all changes required. If a variation is the result of, or if correlated with another variation, a description of the relationship between these changes should be provided in the appropriate section of the application form. In case the change is unclassified, a detailed justification should be included for its request as a Type IB variation;

e) the reference to the section in the Commission Classification Guideline or the reference to the recommendation published in accordance with Art. 5 of the Variations Regulation, used for the respective request, if needed;

f) all documents supporting the variation including any type of document stated in the Commission Classification Guideline as well as the letters for approval of variations in the EU or other EU Member States, if needed;

g) for variations emerging in result of the changes requested by the NAMMD, following the new data submitted, e.g. data triggered by the conditions after the grant of the authorisation or in the context of pharmacovigilance-related obligations, a copy of NAMMD request should be attached to the cover letter;

h) in case the changes affect product information: the revised product information, submitted in the adequate format. In case the design and readability of primary and secondary packagings or of the leaflet are affected by a type IB variation, drafts or samples should be provided in accordance with the Notice to Applicants, volume 2A, Chapter 7, or in accordance with discussions with the NAMMD, on a case-by-case basis.

Art. 35. - At least 15 days prior to the submission of the documents indicated under Art. 34 c) - h), the holder submits to the NAMMD a cover letter and a filled-in fee form.

Art. 36. - Seven days after the submission of the application, the NAMMD assesses the validity of the submitted data (classification of changes as Type IB variation, accurate and complete presentation of data) and informs the holder about the validation/invalidation of the application, while forwarding the grounds for invalidation, requests for supplementation or the date of the start of the assessment procedure (timetable), as required.

Art. 37. – If the proposed change is not considered a Type IB variation in accordance with the Commission Classification Guideline, or if it has not been classified as a Type IB variation in the context of a recommendation according to Art. 5 of the Variations Regulation and if the NAMMD considers this to have potential serious impact upon the quality, safety and efficacy of the medicinal product, the holder is duly informed thereof and required to revise and fill in the application for variation in order to be compliant with the requirements concerning a Type II change.

Art. 38. – 30 days as of the onset of the assessment procedure, in accordance with the agreed calendar, the holder is informed in writing by the NAMMD about the approval/refusal of the NAMMD, in view of completion of the support documentation.

Art. 39. – If objections are raised to Type IB applications for variation, the holder shall respond to these objections within 30 days as of their receipt, while the procedure is stopped until the submission of additional information as required by the NAMMD.

Art. 40. – In case the holder does not forward the required documents within the timeframe mentioned under Art. 39, the application is refused.

Art. 41. - 30 days as of the onset of the assessment procedure, in accordance with the agreed calendar, the holder is informed by the NAMMD in writing about the final approval/refusal of the variation and about the grounds for refusal, if required.

Art. 42. – In case of grouped variations, the NAMMD explicitly informs the holder about the approval/refusal of each variation included in the group.

Art. 43. - The refusal does not affect the right of the holder to resubmit the application for variation.

Art. 44. - If the NAMMD has not issued any objections within the timeframe established under Art. 38 and 41, the application is considered approved.

Art. 45. - Type IB variations may be implemented by the holder immediately after their approval by the NAMMD.

Art. 46. – In case changes to marketing authorisation are required, this is updated by the NAMMD, within 6 months as of date of notification of variation approval.

CHAPTER VII
Administrative procedure for the handling of Type II variations to the terms of Marketing Authorisation

Art. 47. – In case of a Type II variation, prior to the implementation of changes, the holder submits to the NAMMD an application concerning the items mentioned in Annex IV to the Variations Regulation.

Art. 48. – The Variations Regulation and the Commission Classification Guideline establish the changes to be considered Type II variations.

Art. 49. – The application for a Type II variation to the marketing authorisation terms includes:

a) a cover letter;

b) assessment fee payment form;

c) proof of payment of the fee to the NAMMD (copy of the document attesting the encashment of the fee, containing identification data concerning the variation subject to payment);

d) the completed application form concerning variation, including the details of the concerned marketing authorisation(s). In case variation is the result of, or if correlated with another variation, a description of the relationship between

these changes should be provided in the corresponding section of the application form;

e) a reference to the section in the Commission Classification Guideline or a reference to the recommendation published in accordance with Art. 5 of the Variations Regulation, used for the respective request, if needed;

f) all documents supporting the proposed change(s) stated in the Commission Classification Guideline, including the letters for approval of variations in the EU or other EU Member States, if needed;

g) the update or the annexes to quality summaries, nonclinical and clinical summaries, on a case-by-case basis. If summaries of clinical/nonclinical summaries are listed, even if it is just one such report, the respective resume(s) should be included in section 2;

h) for variations emerging in result of the changes requested by the NAMMD, resulted following the new data submitted, e.g. data resulted under the conditions the grant of the authorisation or in the context of pharmacovigilance-related obligations, a copy of NAMMD request should be attached to the cover letter;

i) in case the changes affect the Summary of Product Characteristics, the labelling or the leaflet: the revised product information, presented in the adequate format. In case the design and readability of the secondary and primary packages or of the leaflet are affected by a Type IB variation, drafts and samples should be provided in accordance with the Notice to Applicants, volume 2A, Chapter 7, or according to discussions with the NAMMD, on a case-by-case basis.

Art. 50. - At least 15 days prior to the submission of the documents indicated under Art. 49 c) - i), the holder submits to the NAMMD a cover letter and a filled-in fee form.

Art. 51. – 10 days after the submission of the application, the NAMMD assesses the validity of the submitted application and informs the holder about the validation/invalidation of the application, while forwarding the grounds for invalidation, requests for supplementation or start of the assessment procedure (timetable), as required.

Art. 52. - Generally, 60 days as of the commencement/recommencement of the assessment procedure, in accordance with the agreed calendar, the holder is informed in writing by the NAMMD about the approval/refusal of the variation. This period can be shortened, taking into account the emergency of the issue, particularly as regards safety issues, or it can be extended up to 90 days for the variations on the change or extension of therapeutic indications.

Art. 53. – The letter of refusal of the application for variation includes the grounds for refusal.

Art. 54. – In case of formulating objections for Type II applications for variation, the holder shall respond to objections within 30 days as of their receipt; in this case, the procedure is stopped until the submission of additional

information requested by the NAMMD. Longer suspension periods can be approved by the NAMMD on justified request of the holder.

Art. 55. – If further clarifications are needed following the assessment of documents requested for supplementation, a new 30-60-day period for procedure suspension may be enforced if justified.

Art. 56. – The application for supplementation is accompanied by the modified timetable of the procedure, which shall indicate the deadline for submission of the supplementations performed by the holder.

Art. 57. – In case of grouped variations, the NAMMD explicitly informs the holder about the approval/refusal of each variation included in the group.

Art. 58. – In case the holder does not forward the required documents in due time, as mentioned under Art. 54, the application is considered refused.

Art. 59. – The recall is not detrimental to the holder's right to resubmit the application for variation.

Art. 60. – In case the marketing authorisation requires changes, it is updated by the NAMMD within 60 days as of the notification of the approval of the variation.

Art. 61. - Type II variations may be implemented by the holder 30 days following their approval by the NAMMD.

CHAPTER VIII
Human influenza vaccines

Art. 62. – The changes concerning the annual update of the applications for human influenza vaccines are handled by a special "expedited" procedure which involves two stages:

1. The assessment of administrative and quality data mentioned in Annex IV to the Variations Regulation (the Summary of Product Characteristics, labelling and leaflet, as well as the documentation related to chemical, pharmaceutical and biological issues);

2. The assessment of clinical data and of data concerning the stability of medicinal products.

Art. 63. – Any change brought to human influenza vaccines, other than yearly updates, is compliant with the procedures for handling of variations mentioned in the other chapters of these Norms.

Art. 64. – Holders are advised to discuss with the NAMMD of the yearly updates beforehand.

Art. 65. – The application shall be submitted as follows:

a) cover letter;

b) assessment fee payment form;

c) proof of payment of the fee to the NAMMD (copy of the document attesting the encashment of the fee, containing identification data concerning the variation subject to payment);

d) the update or annex to the quality summary, to the clinical and non-clinical summaries, if relevant. If clinical/non-clinical study reports are presented, even though only one such report is submitted, the related summary(ies) should be included in section 2;

e) chemical-pharmaceutical-biological support data for the proposed change:

(i) a revised expert report for the chemical-pharmaceutical-biological documentation or an annex to the existing expert report. Moreover, the following data is requested:

(ii) the composition of the medicinal product;

(iii) the formulation(s) included in clinical trials: the latest formula (strains);

(iv) manufacturing formula: the latest formula;

(v) a copy of the authorised specifications in tabulated form;

(vi) the manufacturing process:

- batches and strains: history: passage level, the features of hemagglutinin and neuraminidase, analytical protocols (including the results issued from the studies conducted on seed strain batches);

- monovalent batches: the manufacturing process, strain changes, validation of the critical manufacturing stages (new strains; inactivation, efficiency of the division into sections);

(vii) specific quality control testing: validation of the SRD test for new strains;

(viii) results of batch analysis (monovalent batches): results of the first three monovalent batches of each working batch for each new strain (including the neuraminidase test);

(ix) copies of the authorised specifications and of the analytical test methods in tabulated form;

(x) stability tests for the active substances: results for monovalent batches, when used for a period longer than 1 year;

(xi) stability tests for the finished product: results for the preceding vaccines;

(xii) commitment reporting of the data concerning the stability for the new vaccine, if it doesn't correspond to the specifications;

(xiii) annual stability testing protocol;

f) clinical data to support the proposed changes:

(i) expert report for the revised clinical-pharmacological documentation or the annex to the existing expert report;

(ii) the results of clinical trials concerning the new vaccine, forwarded as a short final report, including: primary data, the features of the analysed population (demographics, comorbidity, comedication), standard tables for immunogenicity and reactogenicity. The employed serological test should be clearly stated;

g) the set of clinical data should include the following Periodic Safety Update Reports (PSURs): the PSUR for 1 September - 30 April of the previous

season, the PSUR for 1 May - 31 August of the penultimate season, the revised information about the product, presented in the adequate format.

Art. 66. – At least 15 days prior to the submission of the documents stated under Art. 65 c) - g), the holder submits to the NAMMD the cover letter and the filled-in fee form.

Art. 67. – 7 days as of submission of the application, the NAMMD assesses the validity of the submitted application and informs the holder about the validity of the application or lack thereof, while forwarding the grounds for invalidation, the applications in view of supplementation or date of enforcement of the assessment procedure (schedule), as required.

Art. 68. - 45 days as of the validation of the application for variation, the NAMMD issues a refusal/approval letter for the administrative and quality data concerning the vaccine.

Art. 69. – In case of requests for supplementation of the support documentation with additional data, the holder shall respond to the objections within 7 days as of their receipt; in this case, the procedure is further developed.

Art. 70. – 15 days as of the receipt of the approval letter, the holder submits to the NAMMD the clinical documentation and data concerning the stability of the medicinal product, if required.

Art. 71. – 10 days as of the receipt of the clinical documentation and stability studies, the NAMMD issues the conclusive approval/refusal letter for the variation.

Art. 72. – If the marketing authorisation requires changes, it is updated by the NAMMD.

Art. 73. – In case of a human influenza pandemic, recognized as such by the World Health Organisation or by the European Union, the NAMMD may exceptionally and temporarily take into consideration the approval the approval of a variation to the marketing authorisation terms for influenza vaccines, after the submission of the application and prior to the termination of the procedure.

CHAPTER IX
Urgent Safety Restrictions

Art. 74. – In case of a public health risk from medicinal products for human use, the holder takes interim emergency safety restrictive measures.

Art. 75. – The holder shall inform the NAMMD immediately about the restrictive measures to be introduced.

Art. 76. – If the NAMMD has not issued any complaints 24 hours after having received the information, the safety emergency restrictive measures are considered approved.

Art. 77. – Urgent Safety Restrictions should be enforced in the timeframe jointly agreed upon with the NAMMD.

Art. 78. - Urgent Safety Restrictions may also be imposed by the NAMMD in the event of a public health risk.

Art. 79. – The attached application for variation reflecting the safety emergency restrictive measures (either requested by the holder, or imposed by the NAMMD) shall be forwarded as soon as possible 15 days as of the implementation of the safety emergency restrictive measures.

ANNEX
to the Norms

APPLICATION
for variation to marketing authorisation

- form -

NATIONAL PROCEDURE

TYPE OF VARIATION (check all available options)

- ☐ **Type IA_{IN}**
- ☐ **Tip IA**
- ☐ **Unclassified Type IB variation**[1]
- ☐ **Classified Type IB variation**[1]
- ☐ **Type II variations**
- ☐ **Single variation**
- ☐ **Grouping of variations**

Change(s) envisaged (for Type IA, IB and II variations only, please check all applicable options):

- ☐ **Indication**
- ☐ **Paediatric indication**
- ☐ **Safety**
- ☐ **Following Urgent Safety Restriction**
- ☐ **Quality**
- ☐ **Annual variation for human influenza vaccine**
- ☐ **Other**

[1] A variation is considered "unclassified" when the proposed variation is not a minor variation of Type IB following the Commission classification 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 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.

Name and address of applicant/marketing authorisation holder[2]:	Name and address of the representative/contact person: Telephone number: Fax number: E-mail address:

[2] In accordance with legal information in force.

MEDICINAL PRODUCTS SUBJECT TO THIS APPLICATION[3]

International Non-proprietary Name of the medicinal product(s):	Active substance(s)	Pharmaceutical form	Strength	Marketing Authorisation Holder	Marketing authorisation number(s)[4]

[3]In case this list is extremely lengthy (more than one page), it can be attached as an Annex to the application for variation.

[4] The names of all marketing authorisations subject to this application for variation shall be listed.

TYPE(S) OF CHANGE(S)

☐ Copy of the relevant page(s) from the Commission Classification Guideline is attached; relevant boxes for conditions and documentations are checked.

VARIATIONS INCLUDED IN THIS APPLICATION:

Name and number of the variation, in accordance with the Commission Classification Guideline		**Variation type**
☒	a) Please state the variation subject to this application, in accordance with the Commission Classification Guideline	type

(The variation(s) from the Variations list included in this Annex is/are selected and included in this section, in accordance with the detailed instructions. All inapplicable changes are deleted).

THE EXACT SCOPE AND FRAMEWORK FOR THE CHANGE AND JUSTIFICATION FOR GROUPING AND CLASSIFICATION OF UNCLASSIFIED VARIATIONS (if applicable)
[Please include a brief background description and the framework for all proposed changes. In case of grouping variations, a brief justification is provided in a separate paragraph. If the variation concerns an unclassified change (unprecedented), the justification for its proposed classification is included.]

PRESENT [5,6]	PROPOSED [5,6]

[5] Please specify the present and proposed wording of the text or specification, including the section number in the dossier in the required detail.

[6] For changes in the SPC, labelling and package leaflet, please underline the changed words presented in the table above or provide the data as a separate Annex

OTHER APPLICATIONS[7]

[7] Because of its complexity, filling in this section is not necessary for grouped variations affecting more than one MA.

Type II variations – new therapeutic indication – orphan medicinal product information:

(Please delete this section if not applicable)

HAS ORPHAN DESIGNATION BEEN APPLIED FOR IN RELATION TO 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

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 [8]?

❍ 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, 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 Art. 3 of Regulation (EC) 847/2000 of the Commission in 27 April 2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts "similar medicinal product" and "clinical superiority")*

❍ No (module 1.7.1 to be completed)

❍ Yes (modules 1.7.1 and 1.7.2 to be completed)

[8] As published by the European Commission (http://ec.europa.eu/enterprise/pharmaceuticals/register/index.htm)

Type II variations – Paediatric Requirements:

(Section to be completed only for variations concerning a new indication or for variations related to PIP implementation)

❍ **ARTICLE 8 OF THE PAEDIATRIC REGULATION APPLES TO THIS VARIATION, SINCE:** (NOTE*: Does not apply to medicinal products with well established use, generics, hybrid, biosimilar and herbal medicinal products)*

❍ The application refers to a new therapeutic indication for an authorised medicinal product, which:
❍ is protected by a supplementary protection certificate under Regulation (EEC) No. 1.768/92 of the Council of 18 June 1992 concerning the creation of a supplementary protection certificate for plant protection products
❍ is protected by a patent which qualifies for a granting of the supplementary protection certificate

❍ The application relates to a previous/ongoing parallel procedure, which triggered the Article 8 requirement Procedure number:

❍ **THIS APPLICATION DOES NOT FALL WITHIN THE SCOPE OF ARTICLE 8 OF THE PAEDIATRIC REGULATION.**

❍ **THE APPLICATION RELATES TO A MEDICINAL PRODUCT TO WHICH ART. 7 OF THE PAEDIATRIC REGULATION APPLIES.**

❍ **THE APPLICATION RELATES TO A NEW INDICATION FOR AN AUTHORISED PAEDIATRIC MEDICINAL PRODUCT** (Paediatric Use Marketing Authorisation - PUMA).

❍ **THE APPLICATION RELATES TO PAEDIATRIC STUDIES SUBMITTED ACCORDING TO ART. 45 AND 46 OF THE PAEDIATRIC REGULATION.**

THIS APPLICATION INCLUDES:

❍ PIP Number(s) of PIP decision(s):
❍ Product waiver Waiver decision number:
❍ Class waiver Waiver decision number:

(NOTE*: A copy of the PIP/ waiver decision is to be included in section 1.10.)*

HAS THIS APPLICATION BEEN SUBJECT TO PIP COMPLIANCE VERIFICATION?

❍ No
❍ Yes

If YES, please specify:

❍ PDCO Compliance Opinion Number:

❍ Competent authority document reference:

(NOTE*: If available, a copy of the PDCO opinion accompanied by the report, document issued by the competent authority and the applicant's compliance report is to be included in section 1.10.)*

☐ Please provide the overview table of PIP results in section 1.10.

Type II variations – extension of data exclusivity on the market:
(Blank out this section if not applicable.)

CONSIDERATION OF THIS APPLICATION IS ALSO REQUESTED UNDER THE FOLLOWING ARTICLES OF LAW NO. 95/2006 ON HEALTHCARE REFORM, AS AMENDED, TITLE XVII – THE MEDICINAL PRODUCT:

❍ Article 704 (1) of Law No. 95/2006, as amended, Title XVII (one year of market exclusivity for a new indication)
❍ Article 704 (5) of Law No. 95/2006, as amended, Title XVII (one year of data exclusivity for a new indication)
❍ Article 785 of Law No. 95/2006, as amended, Title XVII (one year of data exclusivity for the change of classification)

(NOTE*: The report justifying the claim for extended data/marketing exclusivity is to be provided in section 1.5.3.)*

Where applicable, the following amended product information text proposals (Annexes) are included:

☐ Summary of Product Characteristics
☐ Labelling
☐ Package Leaflet
☐ Mock-ups [9]
☐ Specimens [9]

_____

[9] See chapter 7 of Volume 2A of the Notice to Applicants.

Declaration of the Applicant:

I hereby submit an application for the above marketing authorisation(s) to be varied in accordance with the proposals given above.

I hereby declare that (*Please check the corresponding statements*):

☐ There are no other changes than those identified in this application (except for those addressed in other variations submitted in parallel; such parallel variations are mentioned in "OTHER APPLICATION(S)").
☐ Where applicable, all conditions set for the variation(s) concerned are met.
☐ For Type IA notifications: the required documents as specified for the changes concerned have been submitted.
☐ The assessment fee has been paid.
☐ In case of grouped variations affecting more than one marketing authorisation: the marketing authorisations belong to the same holder.

The change(s) is enforced as of[10]: ☐

Next manufacturing batch/Next printing

☐ Date ……..

[10] Only to be filled in in case of Type IB and II variations.

LIST OF VARIATIONS (to be deleted after the completion of the application**)**

The applicable variation(s) is selected from this list, as follows:

Only the change(s) subject to this application for variation is included.

In case of (unprecedented) applications for unclassified variations, the applicant should declare these variations as "Other" („z") and use the section included in the list corresponding to the most accurate description of the change, including the type of variation proposed in this case. It is stated whether the variation was subject to a procedure in accordance with Art. 5 of Regulation (EC) No. 1234/2008 of the Commission Regulation (EC) No 1234/2008 of 24 of November 2008, concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products. Examples of such variations are included in the context of a relevant number of variation titles and sections.

In case of Type IA variations, the date of their enforcement is to be stated by the marketing authorisation holder.

Complete details concerning the exact scope of the variation is to be provided in the adequate section of the application.

Examples of presentation :)*

1. Application for changes outside the approved 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	**Variation type**
☒ f) **Change outside the approved specifications limits range for the active substance**	II

2. Application for an unclassified (unprecedented) variation concerning the specified limits for the active substances

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	**Variation**	
☒ z) Other variation	☐*IA* ☐*IB* ☐*II*	☐ *Art 5* **Date of enforcement:**

3. Application for an unclassified (unprecedented) variation concerning the control of the active substance

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

All inapplicable changes are deleted.

*) Examples are reproduced in facsimile.

A. Administrative changes	**Variation type**	
☐ z) Other variation	☐*IA* ☐*IB* ☐*II*	☐ *Art 5* **Date of enforcement:**

		Variation type		
☐ **A.1**	**Change in the name and/or address of the marketing authorisation holder**	☐IA_{NI}	☐IB[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

		Variation type
☐ **A.2**	**Change in the name of the medicinal product**	*IB*

		Variation type		
☐ **A.3**	**Change in the name of the active substance**	☐IA_{NI}	☐IB[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

		Variation type		
☐ **A.4**	**Change in the name and/or address of a manufacturer(including where relevant quality control sites) or supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the product dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier**	☐IA	☐IB[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

A.5 Change in the name and/or address of a manufacturer of the finished product, including quality control sites		**Variation type**		
☐ a)	Manufacturer responsible for batch release	☐IA_{NI}	☐IB[9]	**Date of enforcement:**
☐ b)	All other	☐IA	☐IB[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

		Variation type		
☐ **A.6**	*Change of the ATC code*	☐IA	☐IB[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

		Variation type		
☐ **A.7**	**Deletion of manufacturing sites (including 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[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

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

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 sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	**Variation type**

☐ a)	The proposed manufacturer and the already authorised manufacturer belong to the same pharmaceutical group	☐IA_{NI}	☐IB[9]	**Date of enforcement:**
☐ b)	Introduction of a new manufacturer of the active substance that is 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 certain skills, or physico-chemical properties affecting 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[9]	**Date of enforcement:**
☐ z)	Other variation	☐*IA* ☐*IB* ☐*II*		☐ *Art 5* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.I.a.2 Changes in the manufacturing process of the active substance		**Variation type**		
☐ a)	Minor change in the manufacturing process of the active substance.	☐IA	☐IB[9]	**Date of enforcement:**
☐ 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 relates to a biological/immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol.	*II*		
☐ d)	The change relates to a herbal medicinal product and there is a change to any of the following: geographical source, manufacturing route or production.	*II*		
☐ e)	Minor change to the restricted part of an Active Substance Master File	*IB*		
☐ z)	Other variation	☐*IA* ☐*IB* ☐*II*		☐ *Art 5* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate		**Variation type**		
☐ a)	Up to 10-fold increase compared to the currently approved batch size	☐IA	☐IB[9]	**Date of enforcement:**
☐ b)	Downscaling	☐IA	☐IB[9]	**Date of enforcement:**
☐ c)	The change requires assessment of the comparability of a biological/immunological active substance.	*II*		
☐ d)	More than 10-fold increase compared to the currently 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* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance		**Variation type**		
☐ a)	Tightening of in-process limits	☐IA	☐IB[9]	**Date of enforcement:**
☐ b)	Addition of a new in-process test and limits	☐IA	☐IB[9]	**Date of enforcement:**
☐ c)	Deletion of a non-significant in-process test	☐IA	☐IB[9]	**Date of enforcement:**
☐ 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* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

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

B.I.b Control of active substance		**Variation type**	
☐ z)	Other variation	☐*IA* ☐*IB* ☐*II*	☐ *Art 5* **Date of enforcement:**

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		**Variation type**		
☐ a)	Tightening of specification limits for medicinal products subject to Official Batch Release	☐IA_{NI}	☐IB[9]	**Date of enforcement:**
☐ b)	Tightening of specification limits	☐IA	☐IB[9]	**Date of enforcement:**
☐ c)	Addition of a new specification parameter to the specification with its corresponding test method	☐IA	☐IB[9]	**Date of enforcement:**
☐ d)	Deletion of a non-significant specification parameter(e.g. deletion of an obsolete parameter)	☐IA	☐IB[9]	**Date of enforcement:**
☐ 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 as a result of a safety or quality issue	IB		
☐ z)	Other variation	☐*IA* ☐*IB* ☐*II*		☐ *Art 5* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

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		**Variation type**		
☐ a)	Minor changes to an approved test procedure	☐IA	☐IB[9]	**Date of enforcement:**
☐ 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[9]	**Date of enforcement:**
☐ 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[9]	**Date of enforcement:**
☐ d)	Change (replacement) to a biological/immunological/immunochemical test method or a method using a biological reagent for a biological active substance. e.g. peptide map, glyco-map, etc.	II		
☐ e)	Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate	IB		

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.I.c Change in the closure system of the active substance container		**Variation type**		
☐ z)	Other variation	☐*IA* ☐*IB* ☐*II*		☐ *Art 5* **Date of enforcement:**
B.I.c.1 Change in immediate packaging of the active substance		**Variation type**		
☐ a)	Qualitative and/or quantitative composition	☐IA	☐IB[9]	**Date of enforcement:**
☐ 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* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.I.c.2 Change in the specification parameters and/or limits of the immediate packaging of the active substance		**Variation type**		
☐ a)	Tightening of specification limits	☐IA	☐IB[9]	**Date of enforcement:**
☐ b)	Addition of a new specification parameter to the specification with its corresponding test method	☐IA	☐IB[9]	**Date of enforcement:**
☐ c)	Deletion of a non-significant specification parameter(e.g. deletion of an obsolete parameter)	☐IA	☐IB[9]	**Date of enforcement:**
☐ 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* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.I.c.3 Change in test procedure for the immediate packaging of the active substance			Variation type		
☐	a)	Minor changes to an approved test procedure	☐IA	☐IB[9]	**Date of enforcement:**
☐	b)	Other changes to a test procedure (including replacement or addition)	☐IA	☐IB[9]	**Date of enforcement:**
☐	c)	Deletion of a test procedure if an alternative test procedure is already authorised	☐IA	☐IB[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

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.			Variation type		
	a)	Retesting/storage period			
☐	1.	Reduction	☐IA	☐IB[9]	**Date of enforcement:**
☐	2.	Extension of the retest period based on extrapolation of stability data not in accordance with ICH 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[9]	**Date of enforcement:**
☐	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		
☐	z)	Other variation	☐*IA* ☐*IB* ☐*II*		☐ *Art 5* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.I.e.1 The introduction of a design space or extension of the approved design space, concerning:			Variation 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

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

	Variation type		
B.I.e.3 Deletion of an approved change management protocol related to the active substance	☐IA_{NI}	☐IB[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.a Change in the description and composition of the finished product	Variation type

☐	z)	Other variation	☐*IA* ☐*IB* ☐*II*	☐ *Art 5* **Date of enforcement:**

B.II.a.1 Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking.			**Variation type**		
☐	a)	Changes in imprints, bossing or other markings	☐IA_{NI}	☐IB[9]	**Date of enforcement:**
☐	b)	Changes in scoring/break lines intended to divide into equal doses	IB		
☐	z)	Other variation	☐*IA* ☐*IB* ☐*II*		☐ *Art 5* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.a.2 Change in the shape or dimensions of the pharmaceutical form			**Variation type**		
☐	a)	Immediate release tablets, capsules, suppositories and pessaries	☐IA_{NI}	☐IB[9]	**Date of enforcement:**
☐	b)	Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses	IB		
☐	z)	Other variation	☐*IA* ☐*IB* ☐*II*		☐ *Art 5* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.a.3 Changes in the composition (excipients) of the finished product			**Variation type**		
	a)	Changes in components of the flavouring or colouring system			
☐	1.	Addition, deletion or replacement	☐IA_{NI}	☐IB[9]	**Date of enforcement:**
☐	2.	Increase or reduction	☐IA	☐IB[9]	**Date of enforcement:**
	b)	Other excipients			
☐	1.	Any minor adjustment of the quantitative composition of the finished product with respect to excipients	☐IA	☐IB[9]	**Date of enforcement:**
☐	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 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* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.a.4 Change in coating weight of oral dosage forms or change in weight of capsule shells			**Variation type**		
☐	a)	Solid oral pharmaceutical forms	☐IA	☐IB[9]	**Date of enforcement:**
☐	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 **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

	Variation 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

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

B.II.b Change in the manufacturing process of the finished product			**Variation type**	
☐	z)	Other variation	☐IA ☐IB ☐II	☐ Art 5 **Date of enforcement:**

B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product			**Variation type**		
☐	a)	Secondary packaging site	☐IA_{NI}	☐IB[9]	**Date of enforcement:**
☐	b)	Primary packaging site	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐	c)	Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.	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 sterile medicinal products manufactured using an aseptic method excluding biological/immunological medicinal products.	IB		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ Art 5 **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.b.2 Change to batch release arrangements and quality control testing of the finished product			**Variation type**		
☐	a)	Replacement or addition of a site where batch control/testing takes place	☐IA	☐IB[9]	**Date of enforcement:**
	b)	Replacement or addition of a manufacturer responsible for batch release			
☐	1.	Not including batch control/testing	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐	2.	Including batch control/testing	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐	3.	Including batch control/testing for a biological/immunological product and one of the test methods performed at that site is a biological/immunological/immunochemical method.	II		

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.b.3 Change in the manufacturing process of the finished product			Variation type		
☐	a)	Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions.	☐IA	☐IB[9]	**Date of enforcement:**
☐	b)	Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	II		
☐	c)	The product is a biological/immunological medicinal product and the change requires an assessment of comparability.	II		
☐	d)	Introduction of a non-standard terminal sterilization method	II		
☐	e)	Introduction or increase in the overage that is used for the active substance	II		
☐	f)	Minor change in the manufacturing process of an aqueous oral suspension.	IB		
☐	z)	Other variation	☐*IA* ☐*IB* ☐*II*		☐ *Art 5* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.b.4 Change in the batch size (including batch size ranges) of the finished product			Variation type		
☐	a)	Up to 10-fold compared to the currently approved batch size	☐IA	☐IB[9]	**Date of enforcement:**
☐	b)	Downscaling down to 10-fold	☐IA	☐IB[9]	**Date of enforcement:**
☐	c)	The change requires assessment of the comparability of a biological/immunological medicinal product.	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 currently approved batch size for immediate release	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* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product			Variation type		
☐	a)	Tightening of in-process limits	☐IA	☐IB[9]	**Date of enforcement:**
☐	b)	Addition of a new tests and limits	☐IA	☐IB[9]	**Date of enforcement:**
☐	c)	Deletion of a non-significant in-process test	☐IA	☐IB[9]	**Date of enforcement:**
☐	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 **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.c Control of excipients			**Variation type**	
☐	z)	Other variation	☐IA ☐IB ☐II	☐ Art 5 **Date of enforcement:**

B.II.c.1 Change in the specification parameters and/or limits of an excipient			**Variation type**		
☐	a)	Tightening of specification limits	☐IA	☐IB[9]	**Date of enforcement:**
☐	b)	Addition of a new specification parameter to the specification with its corresponding test method	☐IA	☐IB[9]	**Date of enforcement:**
☐	c)	Deletion of a non-significant specification parameter(e.g. deletion of an obsolete parameter)	☐IA	☐IB[9]	**Date of enforcement:**
☐	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 as a result of a safety or quality issue	IB		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ Art 5 **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.c.2 Change in test procedure for an excipient			**Variation type**		
☐	a)	Minor changes to an approved test procedure	☐IA	☐IB[9]	**Date of enforcement:**
☐	b)	Deletion of a test procedure if an alternative test procedure is already authorised	☐IA	☐IB[9]	**Date of enforcement:**
☐	c)	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		

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.c.3 Change in source of an excipient or reagent with TSE risk			**Variation 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[9]	**Date of enforcement:**
☐	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		

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.c.4 Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier)			**Variation type**		
☐	a)	Minor change in synthesis or recovery of a non-pharmacopoeial excipient	☐IA	☐IB[9]	**Date of enforcement:**

☐	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* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.d Control of finished product			**Variation type**	
☐	z)	Other variation	☐*IA* ☐*IB* ☐*II*	☐ *Art 5* **Date of enforcement:**

B.II.d.1 Change in the specification parameters and/or limits of the finished product			**Variation type**		
☐	a)	Tightening of specification limits	☐IA	☐IB[9]	**Date of enforcement:**
☐	b)	Tightening of specification limits for medicinal products subject to Official Batch Release	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐	c)	Addition of a new specification parameter to the specification with its corresponding test method	☐IA	☐IB[9]	**Date of enforcement:**
☐	d)	Deletion of a non-significant specification parameter(e.g. deletion of an obsolete parameter	☐IA	☐IB[9]	**Date of enforcement:**
☐	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 as a result of a safety or quality issue	IB		
☐	z)	Other variation	☐*IA* ☐*IB* ☐*II*		☐ *Art 5* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.d.2 Change in test procedure for the finished product			**Variation type**		
☐	a)	Minor changes to an approved test procedure	☐IA	☐IB[9]	**Date of enforcement:**
☐	b)	Deletion of a test procedure if an alternative method is already authorised	☐IA	☐IB[9]	**Date of enforcement:**
☐	c)	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		

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

		Variation 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 Container closure system			**Variation type**	
☐	z)	Other variation	☐*IA* ☐*IB* ☐*II*	☐ *Art 5* **Date of enforcement:**

B.II.e.1 Change in immediate packaging of the finished product			**Variation type**		
	a)	Qualitative and quantitative composition			
☐		1. Solid pharmaceutical forms	☐ IA	☐ IB[9]	**Date of enforcement:**
☐		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)	Type of container				
☐	1.	Solid, semi-solid and non-sterile liquid pharmaceutical forms	IB		
☐	2.	Sterile medicinal products and biological/immunological medicinal products	II		
☐ z)	Other variation		☐ *IA* ☐ *IB* ☐ *II*		☐ *Art 5* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.e.2 Change in the specification parameters and/or limits of the immediate packaging of the finished product		**Variation type**		
☐ a)	Tightening of specification limits	☐IA	☐IB[9]	**Date of enforcement:**
☐ b)	Addition of a new specification parameter to the specification with its corresponding test method	☐IA	☐IB[9]	**Date of enforcement:**
☐ c)	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	☐IA	☐IB[9]	**Date of enforcement:**
☐ 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* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.e.3 Change in test procedure for the immediate packaging of the finished product		**Variation type**		
☐ a)	Minor changes to an approved teat procedure	☐IA	☐IB[9]	**Date of enforcement:**
☐ b)	Other changes to a test procedure (including replacement or addition)	☐IA	☐IB[9]	**Date of enforcement:**
☐ c)	Deletion of a test procedure if an alternative test procedure is already authorised	☐IA	☐IB[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging)		**Variation type**		
☐ a)	Non-sterile medicinal products	☐IA	☐IB[9]	**Date of enforcement:**
☐ 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		

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.e.5 Change in pack size of the finished product		**Variation 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[9]	**Date of enforcement:**
☐ 2.	Change outside the range of the currently approved pack sizes	IB		

☐	b)	Deletion of a pack size(s)	☐IA	☐IB[9]	**Date of enforcement:**
☐	c)	Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, and biological/immunological multidose parenteral 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* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

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))**	**Variation type**		
☐	a)	Change that affects the product information	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐	b)	Change that does not affect the product information	☐IA	☐IB[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.e.7		**Change in supplier of packaging components or devices (when mentioned in the dossier)**	**Variation type**		
☐	a)	Deletion of a supplier	☐IA	☐IB[9]	**Date of enforcement:**
☐	b)	Replacement or addition of a supplier	☐IA	☐IB[9]	**Date of enforcement:**
☐	c)	Any change to suppliers of spacer devices for metered dose inhalers	II		

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.f.1			**Change in the shelf-life or storage conditions of the finished product**	**Variation type**		
	a)		Reduction of the shelf life of the finished product			
☐		1.	As packaged for sale	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐		2.	After first opening	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐		3.	After dilution or reconstitution	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
	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 guidelines (*)	II		
☐		5.	Extension of storage period 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		
☐	z)		Other variation	☐*IA* ☐*IB* ☐*II*		☐ *Art 5* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product, excluding biologicals, concerning		Variation 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	Variation type
	II

B.II.g.3 Deletion of an approved change management protocol related to the finish product	Variation type ☐IA_{IN}	☐IB[9]	Date of enforcement:

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.III.1 Submission of a new or updated 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			Variation type		
	a)	European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.			
☐	1.	New certificate from an already approved manufacturer	☐IA_{IN}	☐IB[9]	Date of enforcement:
☐	2.	Updated certificate from an already approved manufacturer	☐IA	☐IB[9]	Date of enforcement:
☐	3.	New certificate from a new manufacturer (replacement or addition)	☐IA_{IN}	☐IB[9]	Date of enforcement:
	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[9]	Date of enforcement:
☐	2.	New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	☐IA	☐IB[9]	Date of enforcement:
☐	3.	Updated certificate from an already approved manufacturer	☐IA	☐IB[9]	Date of enforcement:

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State			Variation type		
	a)	Change of specification(s) of a former non-Pharmacopoeial substance to comply with the Ph.Eur. or with a national pharmacopoeia of a Member State			
☐	1.	Active substance	☐IA_{IN}	☐IB[9]	Date of enforcement:
☐	2.	Excipient/active substance starting material	☐IA	☐IB[9]	Date of enforcement:
☐	b)	Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	☐IA	☐IB[9]	Date of enforcement:
☐	c)	Change in specifications from a national pharmacopoeia of a Member State to the Ph. Eur.	☐IA	☐IB[9]	Date of enforcement:

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.IV Medical devices			Variation type		
☐	z)	Other variation	☐IA ☐IB ☐II		☐ Art 5 **Date of enforcement:**

B.IV.1 Change of a measuring or administration device			Variation 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[9]	**Date of enforcement:**
☐		2. Device without CE marking for veterinary products only	IB		
☐		3. Spacer device for metered dose inhalers	II		
☐	b)	Deletion of a device	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐	c)	Addition or replacement of a device which is an integrated part of the primary packaging	II		

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.IV.2 Not applicable for medicinal products for human use	

B.IV.3 Not applicable for medicinal products for human use	

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)			Variation 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[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

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)			Variation 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[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.V.b.1 Update of the quality dossier following a Commission Decision following the procedure of Article 30 or 31 of Directive 2001/83/EC or Article 34 or 35 of Directive2001/82/EC (referral procedure)			Variation type		
☐	a)	The change implements the outcome of the referral (*)	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐	b)	The harmonisation of the quality dossier was not part of the referral and the update is intended to harmonise it	II		

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

B.V.c.1 Update of the quality dossier to implement changes, requested by the EMEA/National Competent Authority, following assessment of a change management protocol		Variation type		
☐ a)	The implementation of the change requires no further supportive data	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐ b)	The implementation of the change requires further supportive data	IB		
☐ c)	Implementation of a change for a biological/immunological medicinal product	IB		

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

C.I Changes (Safety/Efficacy) in medicinal products for human use		Variation type	
☐ z)	Other variation	☐*IA* ☐*IB* ☐*II*	☐ *Art 5* **Date of enforcement:**

C.I.1 Change in the Summary of Product Characteristics, Labelling or Package Leaflet following a procedure in accordance with Article 30 or 31 of Directive 2001/83/EC or Article 34 or 35 of Directive 2001/82/EC (referral procedure)		Variation type		
☐ a)	The medicinal product is covered by the defined scope of the referral*	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐ b)	The medicinal product is not covered by the defined scope of the referral but the change implements the outcome of the referral and no new additional data are submitted by the MAH	IB		
☐ c)	The medicinal product is not covered by the defined scope of the referral but the change implements the outcome of the referral with new additional data submitted by the MAH	II		

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

C.I.2 Change 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.		Variation type
☐ a)	Implementation of change(s) for which no new additional data are 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 Implementation of change(s) requested by the NAMMD following the assessment of an Urgent Safety Restriction, class labelling, a Periodic Safety Update Report, Risk Management Plan, Follow Up Measure/Specific Obligation, data submitted in accordance with Art. 45 and 46 of Regulation (EC) No. 1901/2006 of the European Parliament and of the Council of 12 December 2006 on paediatric medicinal products and for change of Regulation (EEC) No. 1768/92, of Directive 2001/20/EC, Directive 2001/83/EC and of Regulation (EC) No. 726/2004 or of changes reflecting the main SPC of the competent authority		**Variation type**
☐ a)	Implementation of agreed wording change(s) for which no new additional data are 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	II

	Variation type
C.I.4 Variations related to significant changes of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II

C.I.5 Change in the legal status of a medicinal product for centrally authorised products	Variation type

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

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

C.I.8 Introduction of a new pharmacovigilance system			Variation type
☐	a)	which has not been assessed by the NAMMD for another product of the same MAH	II
☐	b)	which has been assessed by the NAMMD for another product of the same MAH	IB

C.I.9 Changes to an existing pharmacovigilance system as described in the DDPS.			Variation type		
☐	a)	Change in the QPPV	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐	b)	Change in the contact details of the QPPV	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐	c)	Change in the back-up procedure of the QPPV	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐	d)	Change in the safety database (e.g. Introduction of a new safety database including transfer of safety data collection and/or analysis and reporting to the new system)	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐	e)	Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DDPS, in particular where the electronic reporting of ICSRs, the main databases, signal detection, or the compilation of PSURs is subcontracted	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐	f)	Deletion of topics covered by written procedure(s) describing pharmacovigilance activities	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐	g)	Change of the site undertaking pharmacovigilance activities	☐IA_{IN}	☐IB[9]	**Date of enforcement:**
☐	h)	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, update of acronyms, naming changes of functions/procedures).	☐IA	☐IB[9]	**Date of enforcement:**
☐	i)	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[9]	**Date of enforcement:**
☐	z)	Other variation	☐*IA* ☐*IB* ☐*II*		☐ *Art 5* **Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

C.II Not applicable for medicinal products for human use			Variation type

D Changes referring to PMF/VAMF			Variation type	
☐	z)	Other variation	☐*IA* ☐*IB* ☐*II*	☐ *Art 5* **Date of enforcement:**

	Variation type

☐ **D.1 Change in the name and/or address of the VAMF certificate holder**	☐IA_{IN}	☐IB[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

	Variation type		
☐ **D.2 Change in the name and/or address of the PMF certificate holder**	☐IA_{IN}	☐IB[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

	Variation 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[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

	Variation type		
☐ **D.4 Change in the name and/or address of a blood establishment including blood/plasma collection centres**	☐IA	☐IB[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

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

	Variation 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[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

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

	Variation 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

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

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

	Variation type		
☐ **D.11 Deletion of a blood establishment or centre(s) in which storage of plasma is carried out**	☐IA	☐IB[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

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

	Variation type		
☐ **D.13 Deletion of an organisation involved in the transport of plasma**	☐IA	☐IB[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

	Variation 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[9]	**Date of enforcement:**

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

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		**Variation 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[9]	**Date of enforcement:**	

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

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

		Variation type			
☐	**D.17 Introduction or extension of inventory hold procedure**	☐IA	☐IB[9]	**Date of enforcement:**	

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

		Variation 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)		**Variation type**			
☐	a) The new blood containers are EC-marked	☐IA	☐IB[9]	**Date of enforcement:**	
☐	b) The new blood containers are not EC-marked	II			

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

D.20 Change in storage/transport		**Variation type**			
☐	a) Storage and/or transport conditions	☐IA	☐IB[9]	**Date of enforcement:**	
☐	b) Maximum storage time for the plasma	☐IA	☐IB[9]	**Date of enforcement:**	

[9] If one of the conditions is not met and the change is not specifically listed as a Type II variation.

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

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

		Variation 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