DECISION

No. 19/12.08.2013

on approval of the detailed Guideline concerning the various categories of variations to the terms of marketing authorisations and on their examination by the National Agency for Medicines and Medical Devices by the purely national procedure for authorisation of medicinal products for human use, in accordance with Regulation (EC) no. 1234/2008 of the Commission, as amended through Regulation (EU) no. 712/2012

The Scientific Council of the National Agency for Medicines and Medical Devices (NAMMD), established based on Order of the Minister of Health no. 158/18.02.2013, in accordance with Article 8 (1) of the Regulation on the organisation and operation of the NAMMD Scientific Council, hereby adopts through written procedure the following

DECISION

Sole article – The detailed Guideline concerning the various categories of variations to the terms of marketing authorisations and on their examination by the National Agency for Medicines and Medical Devices by the purely national procedure for authorisation of medicinal products for human use, in accordance with Regulation (EC) no. 1234/2008 of the Commission, as amended through Regulation (EU) no. 712/2012 is approved, in accordance with the Annexes which are integral part of this Decision.

PRESIDENT
of the Scientific Council
of the National Agency for Medicines and Medical Devices,

Acad. Prof. Dr. Leonida Gherasim

ANNEX

(SCD no. 19/12.08.2013)

Detailed Guideline concerning the various categories of variations to the terms of marketing authorisations and on their examination by the National Agency for Medicines and Medical Devices by the purely national procedure for authorisation of medicinal products for human use, in accordance with Regulation (EC) no. 1234/2008 of the Commission, as amended through Regulation (EU) no. 712/2012

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CHAPTER I

Introduction

Article 1. – (1) This Guideline is a translation and transposition of *Guideline C(2013) 2804 on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures,* published in the Notice to Applicants *(NTA);* Regulation (EC) no. 1234/2008 of the Commission, hereinafter *The Variations Regulation* has been amended through Regulation (EU) no. 712/2012, which has broadened its scope to medicinal products for human and veterinary use authorised through "purely national" procedure.

(2) The Guideline establishes the procedure of the National Agency for Medicines and Medical Devices, hereinafter the *NAMMD,* for handling of variations to the terms of marketing authorisations of medicinal products for human use, authorised by „purely national" procedure and by the simplified procedures mentioned in 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)].

(3) The „purely national" procedure referred to in this Guideline is the procedure for grant of marketing authorisations by a Member State in accordance with the Community *acquis* conditions outside the Mutual Recognition Procedure.

Article 2. – This Guideline is enforced in accordance with the definitions mentioned in Law 95/2006 on healthcare reform, as amended, Title XVII – The medicinal product, hereinafter the Law, of Regulation (EC) no. 726/2004, as well as those from *The Variations Regulation*.

Article 3. – In accordance with this Guideline, *'variation'* and *'change'* are synonyms, as mentioned in Article 2 (1) of *The Variations Regulation*.

Article 4. – In accordance with this Guideline, applicants belonging to the same mother society or to the same group of societies, as well as applicants who have signed contracts or who have undertaken harmonised practices related to the marketing of the medicinal products concerned should be considered one and the same holder of the marketing authorisation (hereinafter referred to as "holder").

Article 5. - (1) The purpose of this Guideline is to facilitate the interpretation and application of the Variations Regulation and the provision of details on the application of the relevant procedures, including a description of all the relevant steps from the submission of an application for a variation to the final outcome of the procedure on the application.

(2) In addition, Annex 1 to this Guideline provides details of the classification of variations into the following categories as defined in Article 2 of the Variations Regulation: minor variations of Type IA, minor variations of Type IB and major variations of Type II.

(3) It also provides further details, where appropriate, on the scientific data to be submitted for specific variations and how this data should be documented.

(4) Annex 1 to this Guideline will be regularly updated, taking into account the recommendations provided in accordance with Article 5 of the Variations Regulation as well as scientific and technical progress.

CHAPTER II
Recommendations on the handling of variations

Article 6. – A marketing authorisation of a medicinal product in Romania is composed of:

a) a decision granting the marketing authorisation issued by the NAMMD; and

b) a technical dossier with the data submitted by the applicant in accordance with Articles 702 (4) to 708 of the Law, transposing Articles 8(3) to 11 of Directive 2001/83, as well as with Order of the Minister of Health no. 906/2006 on approval of the Analytical, pharmacotoxicological and clinical norms and protocols in respect of the testing of medicinal products, transposing Annex I of Directive 2001/83/EC.

Article 7. - (1) The Variations Regulation governs the procedures for the amendment of the marketing authorisation and of the technical dossier.

(2) However, in the case of medicinal products for human use, the introduction of changes to the labelling or package leaflet that is not connected with the summary of product characteristics is not governed by the procedures of the Variations Regulation.

(3) In accordance with Article 771 (3) of the Law transposing Article 61 (3) of Directive 2001/83, these changes are to be notified to the NAMMD in accordance with the provisions of Order of the Minister of Health no. 1205/2006.

Article 8. - These guidelines cover the following categories of variations, defined in Article 2 of the Variations Regulation:

- Minor variations of Type IA
- Minor variations of Type IB
- Major variations of Type II
- Extensions
- Urgent safety restriction

Article 9. - It must be noticed that where a group of variations consists of different types of variations, the group must be submitted and will be handled according to the 'highest' variation type included in the group; for instance, a group consisting of an extension and a major variation of Type II will be handled as an extension application; a group consisting of minor variations of Type IB and Type IA will be handled as a Type IB notification.

Article 10. - (1) No variation applications for medicinal products undergoing authorisation procedure shall be submitted.

(2) In case of the authorisation procedure, additional documents shall be submitted based on an address for supplementation of the documentation submitted by authorisation procedure.

Article 11. – For grouped variation applications, the fee is established by implementation of the fees for each individual variation, for the variation defining the group (if there are several marketing authorisations for each authorisation in the group affected by the variation) and for each variation included in the group, other than the one defining the group.

Article 12. – The invalidation or request of reclassification of the variation determines the deduction of a percentage of the assessment fee, in accordance with Order of the Minister of Health no. 716/2009 as amended, while the rest remains in the Holder's possession for payment of further services.

Article 13. – Where required, the NAMMD balances the fee for variations to marketing authorisation terms.

Article 14. - The EU application form for variations to a marketing authorisation for medicinal products (human and veterinary) translated into Romanian (Annex 2) is available on the NAMMD website under heading "Forms and fees".

Article 15. - Any information related to the implementation of a given variation should be immediately provided by the holder upon the request of the NAMMD.

II.1 Type IA minor variations

Article 16. - Hereby guidance is provided on the application of Articles 13a, 13d, 13e, 23 and 24 of the Variations Regulation to minor variations of Type IA.

Article 17. - (1) The Variations Regulation and Annex 1 to this Guideline set out a list of changes to be considered as minor variations of Type IA.

(2) Such minor variations do not require any prior approval, but must be notified by the holder within 12 months following implementation ("Do and Tell" procedure).

(3) However, certain minor variations of Type IA require immediate notification after implementation (IAIN), in order to ensure the continuous supervision of the medicinal product.

Article 18. - Annex 1 to this Guideline clarifies the conditions which must be met in order for a variation to follow a Type IA notification procedure, and specifies which minor variations of Type IA must be notified immediately following implementation.

II.1.1. Submission of Type IA variations

Article 19. - (1) Minor variations of Type IA do not require prior examination by the NAMMD before they can be implemented by the holder.

(2) However, at the latest within 12 months from the date of the implementation, the holder must submit simultaneously to the NAMMD a notification of the relevant variation(s).

(3) It is possible for a holder to include a minor variation of Type IA which is not subject to immediate notification in the submission of a minor variation of Type IA for immediate notification or with any other variation.

(4) The conditions laid down in Article 13 (2)(d), a) – c) of the Variations Regulation (as appropriate) should be fulfilled.

Article 20. - The holder may group several minor variations of Type IA under a single notification, as established in Article 13 (2) (d) of the Variations Regulation; specifically, two possibilities exist for the grouping of variations of Type IA:

a) The holder may group several minor variations of Type IA regarding the terms of one single marketing authorisation provided that they are notified at the same time to the NAMMD.

b) The holder may group one or more minor variations of Type IA to the terms of several marketing authorisations under a single notification provided that the variations are the same for all marketing authorisations concerned and they are notified at the same time to the NAMMD.

Article 21. - (1) The 12 months deadline to notify minor variations of Type IA allows holders to collect Type 1A variations for their medicinal products during a year.

(2) However, the notification of these variations in a single submission is only possible where the conditions for grouping apply (same variations for all medicinal products concerned).

(3) Therefore, it may be the case that the submission of variations implemented over a period of 12 months (so called "annual report") requires several submissions; e.g. one referring to a single minor variation of Type IA, another referring to group of minor variations of Type IA to the terms of one marketing authorisation, and another referring to group of the minor variations of Type IA to the terms of several marketing authorisations.

Article 22. - The notification must contain the elements listed in Annex IV to the *Variations Regulation*, presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format and the elements related to the payment of the assessment fee:

a) Cover letter.

b) Payment form of the assessment fee.

c) Proof of payment to the NAMMD (a copy of the document attesting fee payment, containing the identification data of the variation subject to payment);

d) The completed EU variation application form translated into Romanian, including the details of the marketing authorisation(s) concerned, as well as a description of all variations submitted together with their date of implementation as applicable; where a variation is the

consequence of, or related to, another variation, a description of the relation between these variations should be provided in the appropriate section of the application form.

e) Reference to the variation code as laid down in Annex 1 to this Guideline, indicating that all conditions and documentation requirements are met or, where applicable, reference to a classification recommendation published in accordance with Article 5 of the Variation Regulation used for the relevant application.

f) All documentation specified in Annex 1 to this Guideline.

g) In case that the variations affect the summary of product characteristics, labelling or package leaflet: the revised product information presented in the appropriate format, as well as the relevant translations; where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the minor variation of Type IA, mock-ups or specimens should be provided to the NAMMD.

Article 23. - (1) For grouped minor variations of Type IA concerning several marketing authorisations from the same holder in accordance with Article 13d of the Variations Regulation, a common cover letter and application form should be submitted together with separate supportive documentation and revised product information (if applicable) for each medicinal product concerned.

(1) This will allow the NAMMD to update the dossier of each marketing authorisation included in the group with the relevant amended or new information.

Article 24. - At least 15 days prior to submission of the documents mentioned under Article 22 c) - g), the holder should submit to the NAMMD the cover letter and the completed payment form.

II.1.2. Assessment of Type IA variations

Article 25. - The NAMMD will review the Type IA notification within 30 days following receipt.

Article 26. - (1) By Day 30, the NAMMD will inform the holder of the outcome of its review.

(2) In case the marketing authorisation requires any amendment to the decision granting the marketing authorisation, the NAMMD will update the decision granting the marketing authorisation within 6 months following the date of information to the holder of the outcome of the review, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the NAMMD.

Article 27. - Where one or several minor variations of Type IA are submitted as part of one notification, the NAMMD will inform the holder which variation(s) have been accepted or rejected following its review.

Article 28. - (1) While in the case of minor variations of Type IA, failure to provide all necessary documentation in the application will not necessarily lead to the immediate rejection of the variation if the holder provides any missing documentation immediately on request of the NAMMD.

(2) It should be highlighted that a minor variation of Type IA may in specific circumstances be rejected with the consequence that the holder must immediately cease to apply already implemented variations concerned.

II.2. Type IB minor variations

Article 29. - Hereby guidance is provided on the application of Articles 13b, 13d, 13e, 23 and 24 of the Variations Regulation to minor variations of Type IB.

Article 30. - (1) The Variations Regulation and Annex 1 to this Guideline set out a list of changes to be considered as minor variations of Type IB.

(2) Such minor variations must be notified before implementation.

(3) The holder must wait a period of 30 days to ensure that the notification is deemed acceptable by the NAMMD before implementing the change ("Tell, Wait and Do" procedure).

II.2.1. Submission of Type IB notifications

Article 31. - Notifications for minor variations of Type IB must be submitted by the holder to the NAMMD in view of approval.

Article 32. - Holders may group under a single notification the submission of several minor variations of Type IB regarding the same marketing authorisation, or group the submission of one or more minor variation(s) of Type IB with other minor variations regarding the same marketing authorisation, provided that this corresponds to one of the cases listed in Annex III of the Variations Regulation, or when this has been agreed previously with the NAMMD.

Article 33. - In addition, for medicinal products authorised under purely national procedures, the holder may also group several minor variations of Type IB affecting several marketing authorisations released by the NAMMD, or one or more minor variation(s) of Type IB with other minor variations affecting several marketing authorisations released by the NAMMD provided that:

a) the variations are the same for all the marketing authorisations concerned,

b) the variations are submitted at the same time to the NAMMD, and

c) the NAMMD has previously agreed to the grouping.

Article 34. - Furthermore, where the same minor variation of Type IB or the same group of minor variations (as explained above) affect several marketing authorisations owned by the same holder, the holder may submit these variations as one application for 'worksharing' (see Chapter 3 on 'worksharing').

Article 35. - The notification must contain the elements listed in Annex IV to the *Variations Regulation*, presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format, as well as the items related to the payment of the assessment fee:

a) Cover letter;

b) Payment form of the assessment fee;

c) Proof of payment to the NAMMD (a copy of the document attesting fee payment, containing the identification data of the variation subject to payment);

d) The completed EU variation application form (published in the Notice to applicants), translated into Romanian, including the details of the marketing authorisations(s) concerned; where a variation is the consequence of or related to another variation, a description of the relation between these variations should be provided in the appropriate section of the application form; where a variation is considered unclassified, a detailed justification for its submission as a Type IB notification must be included.

e) Reference to the variation code as laid down in Annex 1 to this Guideline, indicating that all conditions and documentation requirements are met or, where applicable, reference to a classification recommendation published in accordance with Article 5 of the Variation Regulation used for the relevant application.

f) Relevant documentation in support of the proposed variation including any documentation specified in Annex 1 to this Guideline.

g) For variations requested by the NAMMD or by another authority resulting from new data submitted e.g. pursuant to post authorisation conditions or in the framework of pharmacovigilance obligations, a copy of the application should be annexed to the cover letter.

h) In case that the variations affect the summary of product characteristics, labelling or package leaflet: the revised product information presented in the appropriate format, as well as the relevant translations. Where the overall design and readability of the outer and immediate

packaging or package leaflet is affected by the minor variation of Type IB, mock-ups or specimens should be provided to the NAMMD.

Article 36. – At least 15 days prior to submission of the documents mentioned under Article 35 c) – the holder should submit to the NAMMD the cover letter and the completed payment form.

II.2.2. Review of type IB variations

Article 37. - (1) When the proposed variation is not considered a minor variation of Type IB following Annex 1 to this Guideline or has not been classified as a minor variation of Type IB in a recommendation pursuant to Article 5 of the *Variations Regulation*, and the NAMMD considers that it may have a significant impact on the quality, safety or efficacy of the medicinal product, the holder is required to review and fill in the application in accordance with the requirements for a major Type II variation.

(2) Following the receipt of a valid, reviewed application for variation, an assessment procedure for a Type II variation shall be inaugurated (see Subsection II.3.2).

Article 38. - When the NAMMD is of the opinion that the proposed variation can be considered a minor variation of Type IB, the holder will be informed of the outcome of the validation and of the start date of the procedure.

Article 39. - (1) Within 30 days following the acknowledgement of receipt of a valid notification, the NAMMD will notify the holder of the outcome of the procedure.

(2) If the NAMMD has not sent the holder its opinion on the notification within 30 days following the acknowledgement of receipt of a valid notification, the notification will be deemed acceptable.

Article 40. - (1) In case of an unfavourable outcome, the holder may amend the notification within 30 days to take due account of the grounds for the non-acceptance of the variation. If the holder does not amend the notification within 30 days as requested, the variation will be deemed rejected by the NAMMD.

Article 41. - Within 30 days of receipt of the amended notification, the NAMMD will inform the holder of its final acceptance or rejection of the variation(s) (including the grounds for the unfavourable outcome).

Article 42. - As far as grouped minor variations are concerned, the holder will be informed accordingly by the NAMMD about the variation(s) approved/rejected following assessment.

Article 43. - (1) Where necessary, the NAMMD will update the marketing authorisation within 6 months following approval of the procedure, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the NAMMD.

(2) However, the accepted minor variations of Type IB variation may be implemented without awaiting the update of the marketing authorisation.

II.3. Type II Major variations

Article 44. - Hereby guidance is provided on the application of Articles 13c, 13d, 13e, 23 and 24 of the Variations Regulation to major variations of Type II.

Article 45. - (1) The Variations Regulation and Annex 1 to this Guideline set out a list of changes to be considered as major variations of Type II.

(2) Such major variations require approval of the NAMMD before implementation.

II.3.1. Submission of Type II applications

Article 46. - Notifications for major variations of Type II must be submitted by the holder to the NAMMD in view of approval.

Article 47. - Holders may group under a single notification the submission of several major variations of Type II regarding the same marketing authorisation, or group the submission of one or more major variation(s) of Type II with other minor variations regarding the same marketing authorisation, provided that this corresponds to one of the cases listed in Annex III of the Variations Regulation, or when this has been agreed previously with the NAMMD.

Article 48. - In addition, for medicinal products authorised under purely national procedures, the holder may also group several major variations of Type II affecting several marketing authorisations released by the NAMMD, or one or more major variation(s) of Type II with other minor variations affecting several marketing authorisations released by the NAMMD, provided that:

a) the variations are the same for all the marketing authorisations concerned,

b) the variations are submitted at the same time to the NAMMD,

c) the NAMMD has previously agreed to the grouping.

Article 49. - Furthermore, where the same major variation of Type II or the same group of variations (as explained above) affect several marketing authorisations owned by the same holder, the holder may submit these variations as one application for 'worksharing' (see Chapter III on 'worksharing').

Article 50. - The application must contain the elements listed in Annex IV to the *Variations Regulation*, presented as follows in accordance with the appropriate headings and numbering of the EU-CTD format, as well as the items related to the payment of the assessment fee:

a) cover letter;

b) payment form of the assessment fee;

c) proof for payment to the NAMMD, containing identification data of the variation subject to the fee);

d) The completed EU variation application form (published in the Notice to Applicants), including the details of the marketing authorisation(s) concerned; where a variation is the consequence of or related to another variation, a description of the relation between these variations should be provided in the appropriate section of the application form;

e) Reference to the variation code as laid down in Annex 1 to this Guideline, indicating that all conditions and documentation requirements are met or, where applicable, reference to a classification recommendation published in accordance with Article 5 of the Variation Regulation used for the relevant application;

f) Supporting data relating to the proposed variation(s);

g) An updated version to quality summaries, non-clinical overviews and clinical overviews as relevant; when non-clinical or clinical study reports are submitted, even if only one, their relevant summary(ies) should be included in Module 2.

h) For variations requested by the NAMMD or by another competent authority resulting from new data submitted e.g. pursuant to post authorisation conditions or in the framework of pharmacovigilance obligations, a copy of the request should be annexed to the cover letter.

i) In case that the variations affect the summary of product characteristics, labelling or package leaflet, the revised product information presented in the appropriate format, as well as the relevant translations; where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the major variation of Type II, mock-ups or specimens should be provided to the NAMMD.

Article 51. – At least 15 days prior to submission of the documents indicated under Article 50 c) - i), the holder submits to the NAMMD the cover letter and the completed payment form.

II.3.2. Assessment of type II variations

Article 52. - Upon receipt of a Type II application, the NAMMD will handle the application as follows:

Article 53. - (1) If the application contains the elements the elements listed in subsection II.3.1, the NAMMD assesses the validity of the submitted application and notifies the holder about the validation/invalidation of the application, also stating the grounds for invalidation or the date of onset of the assessment procedure, as required.

(2) The procedure starts from the date of acknowledgement of the receipt of a valid application. The holder will be informed of the timetable at the start of the procedure.

Article 54. - As a general rule, for major variations of Type II, a 60-day evaluation period will apply; this period may be reduced by the NAMMD having regard to the urgency of the matter, particularly for safety issues, or may be extended to 90 days for variations listed in Part I of Annex V or for grouping of variations in accordance with Article 13 d) (2)(c) of the Variations Regulation. For variations for veterinary medicinal products listed in Part 2 of Annex V of the Variations Regulation a 90-day period will apply.

The reference Member State will prepare a draft assessment report and a decision on the application according to the communicated timetable and will circulate them to the concerned Member States for comments as well as to the holder for information.

Article 55. - (1) Throughout the evaluation period, the NAMMD may request the holder to provide additional information.

(2) The request for supplementary information will be sent to the holder together with a timetable stating the date by when the holder should submit the requested data and where appropriate the extended evaluation period.

Article 56. - (1) The procedure will be suspended until the receipt of the supplementary information.

(2) In general, a suspension of one month will typically apply.

(3) For longer suspension the holder should send a justified request to the NAMMD for agreement.

Article 57. - The evaluation of responses may take up to 30 or 60 days depending on the complexity and amount of data requested to the holder.

II.3.3. Outcome of assessment of type II variations

Article 58. - By the end of the evaluation period, the NAMMD will finalise and submit the assessment report and its decision on the application, and notifies the holder about the approval or rejection of the variation(s) (while stating the grounds for rejection).

Article 59. - (1) Where several Type II variations, or a group of Type II variation(s) with other minor variations have been submitted as one application, the NAMMD will inform the holder which variation(s) have been accepted or rejected.

(2) The holder may withdraw single variations from the grouped application during the procedure (prior to the finalisation of the assessment performed by the NAMMD).

Article 60. - After approval of the variation(s), the NAMMD will, where necessary, amend the marketing authorisation to reflect the variation(s) within 2 months, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the NAMMD.

Article 61. - The accepted major variation(s) of Type II can be implemented after the holder has been informed about the acceptance of the variation(s) by the NAMMD, provided that the necessary documents to amend the marketing authorisation have been submitted to the Member State concerned.

Article 62. - Variations related to safety issues must be implemented within a time-frame agreed between the NAMMD and the holder.

II.4. Extensions

Article 63. - (1) Annex I of the Variations Regulation sets out a list of changes to be considered as extensions.

(2) As established in Article 19 of the Variations Regulation, such applications will be evaluated in accordance with the same procedure as for the granting of the initial marketing authorisation to which it relates.

(3) The NAMMD approves the extension as a new marketing authorisation.

II.4.1. Submission of applications for extension

Article 64. - Extension applications must be submitted to the NAMMD in view of approval.

Article 65. - (1) Holders may group under a single notification the submission of several extensions, or one or more extensions with one or more other variations, regarding the same marketing authorisation provided that this corresponds to one of the cases listed in Annex III of the Variations Regulation, or when this has been agreed previously with the NAMMD.

(2) However, no worksharing of extensions applications is foreseen in the Variations Regulation.

Article 66. – The application must contain the following elements, as well as elements related to the payment of the fee for assessment of line extension in accordance with the appropriate headings and numbering of the EU-CTD format:

a) cover letter;

b) payment form of the assessment fee;

c) Proof of payment to the NAMMD (a copy of the document attesting fee payment, containing the identification data of the variation subject to payment);

d) The completed EU variation application form (published in the Notice to Applicants) accompanied, if required, by the completed European form for application for variation translated into Romanian, containing the details of the initial marketing authorisation as specified by the line extension;

e) Supporting data relating to the proposed extension; some guidance on the appropriate additional studies required for extension applications is available in Appendix IV to Chapter 1 of Volume 2A or 6A of the Notice to applicants.

f) A full Module 1 should be provided, with justifications for absence of data or documents included in the relevant section(s) of Module 1 or Part 1.

g) Update of quality summaries, non-clinical and clinical overviews, as relevant; when non-clinical or clinical study reports are submitted, even if only one, their relevant summary(ies) should be included in Module 2.

h) In case that the extension affects the summary of product characteristics, labelling or package leaflet: the revised product information, presented in the appropriate format.

Article 67. – The holder submits to the NAMMD the documents shown under Article 66 in accordance with the provisions of Order of the Minister of Health no. 1448/2010 on amendment of the Annex of Order of the Minister of Health no. 895/2006 on approval of the Regulations on marketing authorisation and surveillance of medicinal products for human use.

II.4.2. Assessment of extension

Article 68. - Upon receipt of an extension application under the purely national procedure, it will be handled as an initial marketing authorisation application in accordance with the provisions of the Law and Order of the Minister of Health no. 906/2006.

II.5. Human influenza vaccines

Article 69. - Hereby guidance is provided on the application of Article 13f of the Variations Regulation to the annual update of human influenza vaccines.

Article 70. - (1) Because of the specificities inherent in the manufacturing of human influenza vaccines, a special ‘fast track’ variation procedure is applicable for the annual change in active substance for the purpose of the annual update of a human influenza vaccine in order

to meet the EU recommendation for human influenza virus strain(s) vaccine composition for the coming season.

(2) In addition, a special urgent procedure is foreseen in Article 21 of the Variations Regulation for cases of pandemic situation.

Article 71. - Any other variations to human influenza vaccines follows the variation procedures foreseen in other sections of these Guidelines.

Article 72. - The 'fast track' procedure consists of two steps:

a) The first step concerns the assessment of the administrative and quality data elements (summary of product characteristics, labelling and package leaflet, and the chemical, pharmaceutical and biological documentation).

b) The second step concerns the assessment of additional data where necessary.

Article 73. - Marketing authorisation holders are advised to discuss the annual update submissions in advance with the NAMMD.

II.5.1. Submission of variations for annual update of human influenza vaccines applications

Article 74. - Variations concerning changes to the active substance for the annual update of human influenza vaccines applications must be submitted to the NAMMD for approval.

Article 75. - The application must be presented in accordance with the appropriate headings and numbering of the EU-CTD format, as well as with the aspects related to the assessment fee:

a) Cover letter;

b) Payment form of the assessment fee;

c) Proof for payment to the NAMMD, containing identification data of the variation subject to the fee);

d) The completed EU variation application form translated into Romanian, containing the details of the concerned marketing authorisation(s);

e) Update to quality summaries, non-clinical overviews and clinical overviews as relevant; when non-clinical or clinical study reports are submitted, even if only one, their relevant summary(ies) should be included in Module 2;

f) Supporting data relating to the proposed variation(s).

g) The revised product information, presented in the appropriate format.

Article 76. - At least 15 days prior to submission of the documents indicated in Article 75 c) - g), the holder submits to the NAMMD a cover letter and the completed fee form.

II.5.2. Assessment of variations for the yearly update of influenza vaccines for human use

Article 77. - Upon receipt of an application for the annual update, the NAMMD will handle the application as follows:

Article 78. - The NAMMD will acknowledge receipt of a valid application of an annual variation human influenza vaccine and inform the holder accordingly about the validation (invalidation) of the application, while stating the grounds for invalidation or the date of onset of the assessment procedure, as required.

Article 79. - Within the evaluation period, the NAMMD may send the holder a request for supplementary information (notably clinical or stability data); in such a case, the 45 days deadline is stopped until the requested information has been submitted by the holder.

Article 80. - Within 45 days from the receipt of a valid application, the NAMMD will finalise the evaluation including its decision on the application and inform the holder about the approval or rejection of the variation(s) (including the grounds for the unfavourable outcome).

Article 81. – Upon approval of the variation(s), the NAMMD changes the marketing authorisation(s) in view of including the concerned approved variation(s), provided that the required documents for change of the marketing authorisation are sent beforehand.

II.6 Urgent safety restrictions

Article 82. - Article 22 of the Variations Regulation foresees that in the event of a risk to public health in the case of medicinal products for human use, the holder may take provisional "urgent safety restrictions".

Article 83. - (1) Urgent safety restrictions concern interim variation(s) in the terms of the marketing authorisation due to new information having a bearing on the safe use of the medicinal product.

(2) These urgent variations must be subsequently introduced via a corresponding variation in the marketing authorisation.

Article 84. - The holder must immediately notify the NAMMD of the restrictions to be introduced.

Article 85. - (1) If no objections have been raised by the NAMMD within 24 hours following receipt of that information, the urgent safety restrictions are deemed accepted.

(2) The NAMMD notifies the holder about the approval of urgent safety restrictions.

(3) They must be implemented within a time frame agreed between the NAMMD and the holder.

Article 86. - Urgent safety restrictions may also be imposed by the NAMMD in the event of a risk to public health in the case of medicinal products for human use.

Article 87. - The corresponding variation application reflecting the urgent safety restrictions (whether requested by the holder or imposed by the NAMMD) must be submitted by the holder as soon as possible within 15 days.

Article 88. – Within 24 hours as of NAMMD approval of the urgent safety restrictions, the holder submits to the NAMMD a cover letter and the completed fee form.

II.7. Statement of compliance under the Paediatric Regulation

Article 89. - Regulation (EC) No 1901/2006 on medicinal products for paediatric use and amending Regulation (EEC) no. 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004[1] ("Paediatric Regulation") provides for rewards:

- Under Article 36(1) of Regulation (EC) No 1901/2006, the holder of a patent or supplementary protection certificate is entitled to a six-month extension of the period referred to in Articles 13(1) and 13(2) of Regulation (EEC) no. 1768/92[2] [now: Regulation (EC) no. 469/2009] under certain conditions, including the addition to the marketing authorisation of the statement referred to in Article 28(3) of the Paediatric Regulation ("compliance statement").

Article 90. - It follows that, for the purposes of benefiting from the rewards provided for under Articles 36 of the Paediatric Regulation, a variation to add the compliance statement in the marketing authorisation may be required.

Article 91. - (1) Article 23a of the Variations Regulation simplifies the procedure to add the compliance statement in the marketing authorisation so that the rewards foreseen under Regulation (EC) 1901/2006 may be sought as soon as possible once the requirements foreseen in the Paediatric Regulation have been complied with.

(2) Specifically, in order to include the compliance statement holders should submit a variation request to the NAMMD.

(3) After verification that all relevant conditions are met, the compliance statement is to be included by the NAMMD in the technical dossier of the marketing authorisation.

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1 JO L 378, 27.12.2006, p. 1.

2 From 6 July 2009, this Regulation has been repealed by Regulation (EC) No 469/2009.

Article 92. - For the purposes of legal certainty, the NAMMD will provide the holder with a confirmation that the compliance statement has been included in the technical dossier within 30 days after the relevant assessment has been concluded.

CHAPTER III
Procedural guidance on worksharing

Article 93. - Article 20 of the Variations Regulation allows a holder to submit in one application the same Type IB, the same Type II variation, or the same group of variations corresponding to one of the cases listed in Annex III of the Regulation or agreed with the NAMMD which does not contain any extension affecting:

- (i) more than one purely national marketing authorisation of the same holder in more than one Member State; or
- (ii) one or several purely national marketing authorisations and one or several centralised marketing authorisations of the same holder; or
- (iii) one or several purely national marketing authorisation(s) and one or several mutual recognition marketing authorisation(s) of the same holder; or
- (iv) one or several purely national marketing authorisation(s), one or several mutual recognition marketing authorisation(s) and one or several centralised marketing authorisation(s) of the same holder.

Article 94. - In order to avoid duplication of work in the evaluation of such variations, a worksharing procedure has been established under which one authority (the 'reference authority'), chosen amongst the competent authorities of the Member States, namely by the European Medicines Agency (hereinafter 'Agency'), will examine the variation on behalf of the other concerned authorities.

Article 95. - (1) Where at least one of the concerned marketing authorisations has been authorised via the centralised procedure, the Agency will be the reference authority (section 3.4).

(2) In all other cases, a national competent authority chosen by the coordination group, taking into account the recommendation of the holder, will act as the reference authority (section 3.2).

Article 96. - In order to facilitate the planning of the procedure, holders are encouraged to inform the Agency or the coordination group and the proposed reference authority in advance of the submission of a variation or group of variations to be subject to a worksharing procedure.

Article 97. - (1) In order to benefit from a worksharing procedure, it is necessary that the same change(s) will apply to the different medicinal products concerned with no need (or limited need) for assessment of a potential product-specific impact.

(2) Therefore, where the 'same' change(s) to different marketing authorisations require the submission of individual supportive data for specific medicinal products concerned or separate product-specific assessment, such changes cannot benefit from worksharing.

III.1. Submission of variation(s) application under worksharing

Article 98. - (1) A variation or group of variations presented for worksharing shall be submitted as shown under sections 2.2 and 2.3 concerning minor variations of Type IB and II of the *Guideline C(2013) 2804 on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of 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 and on the documentation to be submitted pursuant to those procedures* and must be transmitted as one integrated submission package covering all variations for all medicinal products.

(2) This must include a common cover letter and application form, together with separate supportive documentation for each medicinal product concerned and revised product information (if applicable) for each medicinal product concerned.

(3) This will allow the Agency, the NAMMD and the national competent authorities to update the dossier of each marketing authorisation included in the worksharing procedure with the relevant amended or new information.

Article 99. - The worksharing application must be submitted to all relevant authorities, i.e. the NAMMD and all Member States where the products concerned are authorised and the NAMMD and all Member States where the products concerned are authorised and the Agency (for the centralised procedure).

III.2. Worksharing assessment not involving medicinal products authorised under the centralised procedure

Article 100. - (1) When the holder informs the coordination group of an upcoming worksharing procedure that does not affect any centralised marketing authorisation, the coordination group will at the next meeting decide on the reference authority, taking into account the proposal of the holder and, if applicable pursuant to the third subparagraph of Article 20(3) of the Variations Regulation, another relevant authority to assist the reference authority.

(2) The holder will be informed by the coordination group of the decision of which national competent authority will act as reference authority.

Article 101 - Upon receipt of a worksharing application, the reference authority will handle the application as follows:

Article 102. - (1) The reference authority will acknowledge receipt of a valid application for worksharing.

(2) Immediately after acknowledging receipt of a valid application, the reference authority will start the procedure.

(3) The holder and the Member States concerned will be informed of the timetable at the start of the procedure.

Article 103. - (1) As a general rule, worksharing procedures will follow a 60-day period or a 90-day evaluation period for variations listed in Part 2 of Annex V of the Variations Regulation.

(2) This period may however be reduced by the reference authority having regard to the urgency of the matter, particularly for safety issues, or may be extended to 90 days for variations listed in Part 1 of Annex V or for grouping of variations in accordance with Article 7(2)(c) or Article 13d(2)(c) of the Variations Regulation.

Article 104. - (1) The reference authority will prepare an opinion according to the communicated timetable and will circulate it to the concerned Member States for comments as well as to the holder for information.

(2) Concerned Member States will send their comments within the deadlines set out in the timetable.

Article 105. - (1) Within the evaluation period, the reference Member State may request the marketing authorisation holder to provide supplementary information.

(2) The request for supplementary information will be sent to the holder together with a timetable stating the date by when the holder should submit the requested data and, where appropriate, the extended evaluation period.

(3) In general, a suspension of one month will typically apply.

(4) For longer suspension the holder should send a justified request to the reference Member State for agreement.

Article 106. - (1) The procedure will be suspended until the receipt of the supplementary information.

(2) The assessment of responses may take up to 30 or 60 days depending on the complexity and amount of data requested to the holder.

Article 107. - After receipt of the holder's response, the reference Member State will finalise the draft opinion and will circulate it to the concerned Member States for comments as well as to the holder for information.

III.3. Outcome of the worksharing assessment not involving medicinal products authorised through the centralised procedure

Article 108. - By the end of the evaluation period, the reference authority will issue its opinion on the application and inform the concerned Member States and the holder.

Article 109. - (1) In case of a favourable opinion, the list of variations that are not considered approvable should be attached in the Opinion (if applicable).

(2) Variations may be considered approvable for some of the concerned products only.

(3) In case of an unfavourable outcome, the grounds for the unfavourable outcome should be explained.

Article 110. - (1) Within 30 days following receipt of the opinion, the concerned Member States will recognise the opinion and inform the reference Member State accordingly, unless a potential serious risk to public health is identified that prevents a Member State from recognising the opinion of the reference Member State.

(2) The Member State that, within 30 days following receipt of the opinion of the reference Member State, identifies such a potential serious risk should inform the reference Member State and give a detailed statement of the reasons for its position.

Article 111. - (1) The reference authority will then refer the application to the coordination group for application of Article 33 (3), (4) and (5) of the Law transposing Article 29 (3), (4) and (5) of Directive 2001/83/EC to the matter of disagreement and will inform the holder and the Member States concerned accordingly.

(2) The holder is not entitled to trigger a referral.

Article 112. - Where a referral to the coordination group is made, the procedure concerning the decision on the worksharing application will be suspended until a decision has been adopted on the referral procedure (including, where relevant, the referral to the Committee for Medicinal Products for Human Use, hereinafter the Committee, in accordance with Articles 32 to 34 of Directive 2001/83/EC).

Article 113. - After a positive opinion is communicated regarding variations with changes to the summary of product characteristics, labelling or package leaflet, the holder should submit, within 7 days, translations of the product information texts to the NAMMD and to all Member States concerned.

Article 114. - Within 30 days following the approval of the opinion or, where a referral has been triggered, the notification of the agreement of the coordination group or the European Commission decision (as applicable), the NAMMD and the other Member States will amend the marketing authorisation(s) accordingly, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the NAMMD and to the other Member States concerned.

Article 115. - Minor variation(s) of Type IB approved via a worksharing procedure, may be implemented upon receipt of the favourable opinion of the reference authority.

Article 116. - Major variation(s) of Type II (including those which contain grouped minor variation(s) of Type IB) approved via a worksharing procedure may be implemented 30 days after receipt of the favourable opinion from the reference authority provided that the necessary documentation to amend the marketing authorisation has been submitted to the Member States concerned.

Article 117. - In those cases where the application has been the object of a referral, the variation(s) must not be implemented until the referral procedure has concluded that the variation(s) is accepted.

Article 118. - Variations related to safety issues must be implemented within a time-frame agreed between the marketing authorisation holder and the reference authority.

III.4. Worksharing assessment involving medicinal products authorised under the centralised procedure

Article 119. - Upon receipt of a worksharing application that affects at least one centralised marketing authorisation, the Agency will handle the application as follows:

Article 120. - (1) The Agency will acknowledge receipt of a valid worksharing application.

(2) Immediately after acknowledging the receipt of a valid application, the Agency will start the procedure.

(3) The holder will be informed of the adopted timetable at the start of the procedure.

Article 121. - The Agency will appoint a rapporteur (and in some cases also a co-rapporteur) to lead the assessment procedure.

Article 122. - (1) In general, worksharing procedures will follow a 60-day evaluation timetable or a 90-day evaluation timetable for variations listed in Part 2 of Annex V of the *Variations Regulation.*

(2) This period may however be reduced by the reference authority having regard to the urgency of the matter, particularly for safety issues, or may be extended to 90 days for variations listed in Part 1 of Annex V or for grouping of variations in accordance with Article 7(2)(c) or Article 13d(2)(c).

Article 123. - (1) Within the evaluation period, the Committee may request supplementary information.

(2) The request for supplementary information or follow-on request will be sent to the holder together with the timetable stating the date by when the holder should submit the requested data and where appropriate the extended evaluation period.

Article 124. - (1) The procedure will be suspended until the receipt of the supplementary information.

(2) In general, a suspension of up to 1 month will typically apply.

(3) For suspension longer than 1 month the holder should send a justified request to the Agency for agreement by the Committee.

Article 125. - For any follow-on request for supplementary information, an additional clock-stop of up to 1 month will be applied in general; a maximum of 2 months may be applied when justified.

Article 126. - The Committee assessment of responses may take up to 30 or 60 days depending on the complexity and amount of data provided by the marketing authorisation holder.

Article 127. - An oral explanation can be held at the request of the relevant Committee or the marketing authorisation holder, where appropriate.

III.5. Outcome of the worksharing assessment involving medicinal products authorised through the centralised procedure

Article 128. - (1) By the end of the evaluation period, the Agency will adopt an opinion on the application, including the assessment report.

(2) The Agency will inform the holder and Member States concerned (if applicable).

(3) In case of disagreement with the opinion, holders may request a re-examination thereof in accordance with the procedure set out in Article 9 (2) and 34 (2) of Regulation (EC) No 726/2004.

Article 129. - Where the opinion of the Agency is favourable and the variation(s) affects the terms of the Commission decision(s) granting the marketing authorisation, the Agency will transmit to the Commission its opinion and the grounds for its opinion as well as the necessary documents to amend the marketing authorisation.

Article 130. - (1) If the Agency considers that some variations are not approvable, the list of variations that are not considered approvable should be attached in the Opinion.

(2) Variations may be considered approvable for some of the concerned products only.

Article 131. - Upon receipt of a favourable opinion by the NAMMD and by the Member States concerned, for medicinal products authorised under the purely national procedure, the NAMMD and the other interested Member States must approve the opinion, inform the Agency accordingly and, where necessary, amend the national marketing authorisations within 60 days provided that the necessary documents to amend the marketing authorisation(s) have been submitted.

Article 132. - Minor variation(s) of Type IB (with the exception of those grouped with major variation(s) of Type II) may be implemented upon receipt of the favourable opinion of the Agency.

Article 133. - Major variation(s) of Type II (and those minor variation(s) of Type IB grouped with the Type II variation) may be implemented 30 days after receipt of the favourable opinion from the Agency provided that:

a) the documents necessary for the amendment of the marketing authorisation(s) have been submitted to the NAMMD and to Member States concerned, and

b) the application has not been the object of a referral.

CHAPTER IV
ANNEX 1

Article 134. - This Annex consists of four chapters classifying variations related to: A) Administrative changes; B) Quality changes; C) Safety, Efficacy and Pharmacovigilance changes and D) Specific changes to Plasma Master Files (PMF) and Vaccine Antigen Master Files (VAMF).

Article 135. - Where reference has to be made to specific variations in this Annex, the variation(s) in question should be quoted using the following structure: X.N.x.n ("variation code").

– X refers to the capital letter of the chapter in this Annex where the variation is included (e.g. A, B, C or D)

– N refers to the roman number of the section inside a chapter where the variation is included (e.g. I, II, III…)

– x refers to the letter of the subsection inside a chapter where the variation is included (e.g. a, b, c…)

– n refers to the number given in this Annex to a specific variation (e.g. 1, 2, 3…)

Article 136. – For each chapter this Annex contains:

- A list of variations which should be classified as minor variations of Type IA or major variations of Type II in accordance with the definitions of Article 2 and Annex II to the *Variations Regulation*. It is also indicated which minor variations of Type IA require immediate notification as established in Article 8 (1) of the *Variations Regulation*.
- A list of variations that should be considered as minor variations of Type IB. It is noted that, in accordance with Article 3 of the Variations Regulation, this category applies by default. Accordingly, this Annex does not attempt to establish an exhaustive list for this category of variations.

Article 137. - (1) This Annex does not deal with the classification of extensions as they are exhaustively listed in Annex I of the *Variations Regulation.*

(2) All changes specified in Annex I of the *Variations Regulation* must be considered extensions of the marketing authorisations; any other change cannot be classified as such.

Article 138. - When one or more of the conditions established in this Annex for a minor variation of Type IA are not met, the concerned change may be submitted as a Type IB variation ("Type IB by default") unless the change is specifically classified as a major variation of Type II in this Annex or in a recommendation pursuant to Article 5 of the Variations Regulation, or unless the applicant considers that the changes may have a significant impact on the quality, safety or efficacy of the medicinal product.

Article 139. - If the NAMMD considers that a variation submitted as a Type IB by default may have a significant impact on the quality, safety or efficacy of the medicinal product, it may request that the application be upgraded and processed as a Type II variation.

Article 140. - (1) For the purpose of this Annex “test procedure” has the same meaning as “analytical procedure”; “limits” has the same meaning as “acceptance criteria”.

(2) “Specification parameter” means the quality attribute for which a test procedure and limits are set e.g. assay, identity, water content.

(3) The addition or deletion of a specification parameter therefore includes its corresponding test method and limits.

Article 141. - When several minor changes are taking place (e.g. to the same method or process or material) at the same time or in cases of a major update of the quality information for the active substance or the finished product, the applicant should take into account the overall impact of these changes on the quality, safety or efficacy of the medicinal product when considering the appropriate classification and submit them accordingly.

Article 142. - Specific supporting data for Type IB and Type II variations will depend on the specific nature of the change.

Article 143. - (1) Furthermore, if a variation leads to a revision of the summary of product characteristics, labelling or package leaflet (jointly referred to as ‘the product information’), this change is considered part of that variation.

(2) In such cases updated product information has to be submitted as part of the application with the relevant translations.

(3) Mock-ups or specimens should be provided to the NAMMD.

Article 144. - (1) There is no need to notify the NAMMD of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that reference is made to the ‘current edition’ in the dossier of an authorised medicinal product.

(2) Applicants are reminded that compliance with the updated monograph should be implemented within six months.

Article 145. – (1) Any change to the content of the dossier that supports a European Pharmacopoeia Certificate of Suitability, should be submitted to the European Directorate for the Quality of Medicines (EDQM).

(2) However, if the certificate is revised following EDQM evaluation of this change, any marketing authorisation concerned must be updated accordingly.

Article 146. - (1) With reference to Section 1, ‘Biological medicinal products’ of Part III, ‘Special medicinal products’ of Order of the Minister of Health no. 906/2006 transposing point 1 of Annex I of Directive 2001/83/EC, changes to Plasma Master Files (hereinafter PMFs) and Vaccine Antigen Master Files (VAMFs) follow the evaluation procedures for variations set-out in the Variations Regulation.

(2) Therefore, Chapter D in this guideline provides a list of variations which are specific to such PMFs or VAMFs.

(3) Following review of these variations, any marketing authorisation concerned must be updated in accordance with Chapter B.V of this Annex.

(4) In case the documentation of the human plasma used as starting material for a plasma derived medicinal product is not submitted as a PMF, variations to this starting material as described in the marketing authorisation dossier should also be handled in accordance with this Annex.

Article 147. - (1) References in this Annex to changes to the marketing authorisation dossier mean addition, replacement or deletion, unless specifically indicated.

(2) If amendments to the dossier only concern editorial changes, such changes should generally not be submitted as a separate variation, but they can be included in a variation concerning that part of the dossier. In such cases the changes should be clearly identified in the application form as editorial changes and a declaration that the content of the concerned part of the dossier has not been changed by the editorial changes beyond the scope of the variation submitted should be provided; it should be noted that editorial changes include the removal of obsolete or redundant text but not the removal of specification parameters or manufacturing descriptions.

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A. ADMINISTRATIVE CHANGES

A.1 Change in the name and/or address of the marketing authorisation holder	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	1, 2	IAIN
Conditions			
1. The marketing authorisation holder shall remain the same legal entity.			
Documentation			
1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.			
2. Revised product information.			

A.2 Change in the (invented) name of the medicinal product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
b) For Nationally Authorised Products		2	IB
Documentation			
1. Revised product information.			

A.3 Change in name of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1, 2	1, 2	IAIN
Conditions			
1. The active substance/excipient shall remain the same.			
Documentation			
1. Proof of acceptance by WHO or copy of the INN list. If required, a proof attesting that the change is in line with the European Pharmacopoeia. For herbal medicinal product, declaration that the name is in accordance with the Note for Guidance on Quality of Herbal Medicinal Products, and with the guideline on declaration of herbal substances and herbal preparations in (traditional) herbal medicinal products.			
2. Revised product information			

A.4 Change in the name and/or address of a manufacturer (including 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; or of a manufacturer of a new excipient (where specified in the product dossier)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	1, 2, 3	IA
Conditions			
1. The manufacturing site and all manufacturing operations shall remain the same.			
Documentation			
1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name and/or address is mentioned.			
2. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
3. In case of change in the name of the holder of the Active Substance Master File holder, updated 'letter of access'.			

A.5 Change in the name and/or address of the manufacturer/importer of the finished product [including the batch release/batch testing site for quality control]	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) The activities for which the manufacturer/importer is responsible include batch release	**1**	**1, 2**	**IAIN**
b) The activities for which the manufacturer/importer is responsible do not include batch release	**1**	**1, 2**	**IA**
Conditions			
1. The manufacturing site undergoing the name and/or address change and all manufacturing operations must remain the same.			
Documentation			
1. Copy of the modified manufacturing authorisation, if available; or a formal document from a relevant official body (e.g. Chamber of Commerce, or if not available, from a Regulatory Agency) in which the new name and/or address is mentioned.			
2. If applicable, amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including revised product information as appropriate.			

A.6 Change in ATC Code / ATC Vet Code	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	**1, 2**	**IA**
Conditions			
1. Change following granting of or amendment to ATC Code by WHO / ATC Vet Code.			
Documentation			
1. Proof of acceptance (by WHO).			
2. Revised product information			

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)*	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1, 2	**1, 2**	**IA**
Conditions			
1. There should at least remain one site/manufacturer, as previously authorised, performing the same function as the one(s) concerned by the deletion. Where applicable at least one manufacturer responsible for batch release that is able to certify the product testing for the purpose of batch release within the EU/EEA remains in the EU/EEA.			
2. The deletion should not be due to critical deficiencies concerning manufacturing.			
Documentation			
1. The variation application form should clearly outline the "present" and "proposed" manufacturers (approved in the context of the marketing authorisation or following a variation).			
2. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including revised product information as appropriate.			
**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 immediately.			

A.8 Changes to date of the audit to verify Good Manufacturing Practice (GMP) compliance of the manufacturer of the active substance*	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
			IA
Documentation			
1. Written confirmation from the manufacturer of the finish product stating verification of compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practices.			
**Note:* This variation does not apply when the information has been otherwise transmitted to the authorities (e.g. through the so-called "QP declaration").			

B. QUALITY CHANGES

B.I ACTIVE SUBSTANCE

B.I.a) Manufacture

B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	**1, 2, 3**	**1, 2, 3, 4, 5, 6, 7**	**IAIN**
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	**2, 4**	**1, 5**	**IA**
g) Introduction of a new manufacturer of the active substance that is not supported by an ASMF and requires significant update to the relevant active substance section of the dossier			**II**
h) Addition of an alternative sterilisation site for the active substance using a Ph.Eur. method		**1, 2, 4, 5, 8**	**IB**
i) Introduction of a new site of micronisation	**2, 5**	**1, 4, 5, 6**	**IA**
j) Changes to quality control testing arrangements for a biological active substance: replacement or addition of a site where batch control/testing including a biological / immunological / immunochemical method takes place			**II**
k) New storage site of Master Cell Bank and/or Working Cell Banks		**1, 5**	**IB**
Conditions			
1. For starting materials and reagents the specifications (including in process controls, methods of analysis of all materials), are identical to those already approved. For intermediates and active substances the specifications (including in process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved.			
2. The active substance is not a biological/immunological substance or sterile.			

3.	Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.*
4.	Method transfer from the old to the new site has been successfully completed.
5.	The particle size specification of the active substance and the corresponding analytical method remain the same.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), if applicable.
2.	A declaration from the marketing authorisation holder or the ASMF holder, where applicable, that the synthetic route (or in case of herbal medicinal products, where appropriate the method of preparation, geographical source, production of herbal drug and manufacturing route) quality control procedures and specifications of the active substance and of the starting material/reagent/intermediate in the manufacturing process of the active substance (if applicable) are the same as those already approved.
3.	Either a TSE Ph. Eur. Certificate of Suitability for any new source of material or, where applicable, documentary evidence that the specific source of the TSE risk material has previously been assessed by the NAMMD and shown to comply with the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*. The information should include the following: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals, its use and previous acceptance.
4.	Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) of the active substance from the current and proposed manufacturers/sites.
5.	The variation application form should clearly outline the "present" and "proposed" manufacturers as listed in section 2.5 of the application form for marketing authorisation.
6.	A declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances - see the note under variation no. B.II.b.1.
7.	Where relevant, a commitment of the manufacturer of the active substance to inform the MA holder of any changes to the manufacturing process, specifications and test procedures of the active substance.
8.	Proof that the proposed site is appropriately authorised for the pharmaceutical form or product or manufacturing operation concerned, i.e.: For a manufacturing site within the EU/EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMP database will suffice. For a manufacturing site outside the EU/EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority. For a manufacturing site outside the EU/EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EU/EEA. A reference to the EudraGMP database will suffice.

B.I.a.2 Changes in the manufacturing process of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Minor change in the manufacturing process of the active substance	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 3**	**IA**
b) Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product			**II**
c) The change refers to a biological / immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological substance, which may have a significant impact on the quality, safety and efficacy of the medicinal product and is not related to a protocol			**II**

d)	The change relates to a herbal medicinal product and there is a change to any of the following: geographical source, manufacturing route or production			**II**
e)	**Minor change to the restricted/closed part of an Active Substance Master File**		**1, 2, 3, 4**	**IB**
Conditions				
1.	No adverse change in qualitative and quantitative impurity profile or in physico-chemical properties.			
2.	The synthetic route remains the same, i.e. intermediates remain the same and there are no new reagents, catalysts or solvents used in the process. In the case of herbal medicinal products, the geographical source, production of the herbal substance and the manufacturing route remain the same.			
3.	The specifications of the active substance or intermediates are unchanged.			
4.	The change is fully described in the open ("applicant's") part of an Active Substance Master File, if applicable.			
5.	The active substance is not a biological / immunological substance.			
6.	The change does not refer to the geographical source, manufacturing route or production of a herbal medicinal product.			
7.	The change does not refer to the restricted part of an Active Substance Master File.			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format) and of the approved Active Substance Master File (where applicable), including a direct comparison of the present process and the new process.			
2.	Batch analysis data (in comparative tabular format) of at least two batches (minimum pilot scale) manufactured according to the currently approved and proposed process.			
3.	Copy of approved specifications of the active substance.			
4.	A declaration from the marketing authorisation holder or the ASMF Holder, where applicable, that there is no change in qualitative and quantitative impurity profile or in physico-chemical properties, that the synthetic route remains the same and that the specifications of the active substance or intermediates are unchanged.			
Note: For B.I.a.2.b For chemical active substances, this refers to substantial changes to the synthetic route or manufacturing conditions which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability.				

B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Up to 10-fold increase compared to the originally approved batch size**	**1, 2, 3, 4, 6, 7, 8**	**1, 2, 5**	**IA**
b)	**Downscaling down to 10-fold**	**1, 2, 3, 4, 5**	**1, 2, 5**	**IA**
c)	**The change requires assessment of the comparability of a biological/immunological active substance**			**II**
d)	**More than 10-fold increase compared to the originally approved batch size**		**1, 2, 3, 4**	**IB**
e)	**The scale for a biological/immunological active substance is increased / decreased without process change (e.g. duplication of line)**		**1, 2, 3, 4**	**IB**
1.	Any changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment.			
2.	Test results of at least two batches according to the specifications should be available for the proposed batch size.			
3.	The product concerned is not a biological/immunological medicinal product.			
4.	The change does not adversely affect the reproducibility of the process.			
5.	The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
6.	The specifications of the active substance/intermediates remain the same.			
7.	The active substance is not sterile.			
8.	The batch size is within the 10-fold range of the batch size foreseen when the marketing authorisation was granted or following a subsequent change not agreed as a Type IA variation.			

Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
2.	The batch numbers of the tested batches having the proposed batch size.
3.	Batch analysis data (in a comparative tabulated format) on a minimum of one production batch of the active substance or intermediate as appropriate, manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).
4.	Copy of approved specifications of the active substance (and of the intermediate, if applicable).
5	A declaration from the marketing authorisation holder or the ASMF holder as appropriate that the changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during manufacture or because of stability concerns and that the specifications of the active substance/intermediates remain the same.

B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Tightening of in-process limits**	**1, 2, 3, 4**	**1, 2**	**IA**
b)	**Addition of a new in-process test and limits**	**1, 2, 5, 6**	**1, 2, 3, 4, 6**	**IA**
c)	**Deletion of a non-significant in-process test**	**1, 2, 7**	**1, 2, 5**	**IA**
d)	**Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the active substance**			**II**
e)	**Deletion of an in-process test which may have a significant effect on the overall quality of the active substance**			**II**
f)	**Addition or replacement of an in-process test as a result of a safety or quality issue**		**1, 2, 3, 4, 6**	**IB**

Conditions	
1.	The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2.	The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits
3.	Any change should be within the range of currently approved limits.
4.	The test procedure remains the same, or changes in the test procedure are minor.
5.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way
6.	The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods)
7.	The specification parameter does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics e.g. particle size, bulk or tapped density, identity test, water, any request for changing the frequency of testing.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
2.	Comparative table of current and proposed in-process tests.
3.	Details of any new non-pharmacopoeial analytical method and validation data, where relevant.
4.	Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the active substance for all specification parameters.
5.	Justification/risk assessment from the marketing authorisation holder or the ASMF Holder, as appropriate, attesting that in-process tests are non-significant, or that the in-process tests are obsolete.
6.	Justification from the MAH or ASMF Holder as appropriate for the new in-process test and limits.

B.I.a.5 Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza	**Conditions to be fulfilled**	**Documentation to be supplied**	**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

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Tightening of specification limits for medicinal products subject to Official Batch Release	**1, 2, 3, 4**	**1, 2**	**IAIN**
b) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
c) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 7**	**IA**
d) Deletion of a non-significant specification parameter(e.g. deletion of an obsolete parameter)	**1, 2, 8**	**1, 2, 6**	**IA**
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product			**II**
f) Change outside the approved specifications limits range for the active substance			**II**
g) Widening of the approved specifications limits for starting materials/intermediates, which may have a significant effect on the overall quality of the active substance and/or the finished product			**II**
h) Addition or replacement (excluding biological or immunological substance) of a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4, 5, 7**	**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		**1, 2, 3, 4, 5, 7**	**IB**

Conditions	
1.	The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2.	The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.
3.	Any change should be within the range of currently approved limits.
4.	The test procedure remains the same, or changes in the test procedure are minor.
5.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6.	The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeia microbiological methods).
7.	For any material, the change does not concern a genotoxic impurity. If it involves the final active substance, other than for residual solvents which must be in line with ICH limits, any new impurity control should be in line with the Ph. Eur. or National Pharmacopoeia of a Member State.
8.	The specification parameter does not concern a critical parameter, for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics e.g. particle size, bulk or tapped density, identity test, water, any request for skip testing.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format
2.	Comparative table of current and proposed specifications.
3.	Details of any new analytical method and validation data, where relevant.
4.	Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the relevant substance for all specification parameters.
5.	Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.

6.	Justification/risk assessment from the marketing authorisation holder or the ASMF Holder, as appropriate, that the in-process parameter is non-significant, or that the in-process parameter is obsolete.
7.	Justification from the MAH or ASMF Holder as appropriate of the new specification parameter and the limits.

B.I.b.2 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Minor changes to an approved test procedure**	**1, 2, 3, 4**	**1, 2**	**IA**
b)	**Deletion of a test procedure for the active substance or a starting material/reagent/intermediate, if an alternative test procedure is already authorised.**	**7**	**1**	**IA**
c)	**Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance**	**1, 2, 3, 5, 6**	**1, 2**	**IA**
d)	**Substantial change to or replacement of a biological/ immunological/ immunochemical test method or a method using a biological reagent for a biological active substance**			**II**
e)	**Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate**		**1, 2**	**IB**

Conditions	
1.	Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.
2.	There have been no changes of the total impurity limits; no new unqualified impurities are detected.
3.	The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
4.	The test method is not a biological/immunological/immunochemical method, or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).
5.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6.	The active substance is not biological/immunological.
7	An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA (IN) notification.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).
2.	Comparative validation results, or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.I.c) Container closure system

B.I.c.1 Change in immediate packaging of the active substance		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Qualitative and/or quantitative composition**	**1, 2, 3**	**1, 2, 3, 4, 6**	**IA**
b)	**Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances**			**II**
c)	**Liquid active substances (non sterile)**		**1, 2, 3, 5, 6**	**IB**

Conditions	
1.	The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.

2.	Relevant stability studies have been started under ICH conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging, the three months' stability data do not yet have to be available. These studies must be finalised and the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the shelf-life/retest period (with proposed action).
3	Sterile, liquid and biological/immunological active substances are excluded.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
2.	Appropriate data on the new packaging (e.g. comparative data on permeability e.g. for O2, CO2, moisture), including a confirmation that the material complies with relevant pharmacopoeial requirements or legislation of the Union on plastic materials and objects in contact with foodstuff.
3.	Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeia requirements or legislation of the Union on plastic material and objects in contact with foodstuff.
4.	A declaration from the marketing authorisation holder or the ASMF holder as appropriate that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
5.	The results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of three months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved retest period (with proposed action).
6.	Comparison of the current and proposed immediate packaging specifications, if applicable.

B.I.c.2 Change in the specification parameters and/or limits of the immediate packaging of the active substance		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Tightening of specification limits**	**1, 2, 3, 4**	**1, 2**	**IA**
b)	**Addition of a new specification parameter to the specification with its corresponding test method**	**1, 2, 5**	**1, 2, 3, 4, 6**	**IA**
c)	**Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)**	**1, 2**	**1, 2, 5**	**IA**
d)	**Addition or replacement of a specification parameter as a result of a safety or quality issue**		**1, 2, 3, 4, 6**	**IB**
Conditions				
1.	The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure) unless it has been previously assessed and agreed as part of a follow-up measure.			
2.	The change does not result from unexpected events arising during manufacture of the packaging material or during storage of the active substance.			
3.	Any change should be within the range of currently approved limits.			
4.	The test procedure remains the same, or changes in the test procedure are minor.			
5.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
2.	Comparative table of current and proposed specifications.			
3.	Details of any new analytical method and validation data, where relevant.			
4.	Batch analysis data on two batches of the immediate packaging for all specification parameters.			
5	Justification/risk-assessment from the marketing authorisation holder or the ASMF Holder, as appropriate, showing that the parameter is non-significant or obsolete.			
6.	Justification from the marketing authorisation holder or the ASMF Holder, as appropriate, of the new specification parameter and the limits.			

B.I.c.3 Change in test procedure for the immediate packaging of the active substance	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) **Minor changes to an approved test procedure**	**1, 2, 3,**	**1, 2**	IA
b) **Other changes to a test procedure (including replacement or addition)**	**1, 3, 4**	**1, 2**	IA
c) **Deletion of a test procedure if an alternative test procedure is already authorised**	**5**	**1**	IA
Conditions			
1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.			
2. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).			
3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
4. The active substance/ finished product is not biological/immunological.			
5. There is still a test procedure registered for the specification parameter and this procedure has not been added through a IA/IA(IN) notification.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a description of the analytical methodology, a summary of validation data.			
2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.			

B.I.d) Stability

B.I.d.1 Change in the 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.	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) Re-test period/storage period			
1. Reduction	**1**	**1, 2, 3**	**IA**
2. Extension of the retest period based on extrapolation of stability data not in accordance with 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		**1, 2, 3**	**IB**
b) Storage conditions			
1. Change to more restrictive storage conditions of the active substance	**1**	**1, 2, 3**	**IA**
2. Change in storage conditions of biological/immunological active substances, when the stability studies have not been performed in accordance with a currently approved stability protocol			**II**
3. Change in storage conditions of the active substance		**1, 2, 3**	**IB**
c) Amendment of an approved stability protocol	**1, 2**	**1, 4**	**IA**
Conditions			
1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
2. The changes do not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format). This must contain results of appropriate real time stability studies, conducted in accordance with the relevant stability guidelines on at least two (three for biological medicinal products) pilot or production scale batches of the			

	active substance in the authorised packaging material and covering the duration of the requested re-test period or requested storage conditions.
2.	Confirmation that stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.
3.	Copy of approved specifications of the active substance.
4.	Justification for the proposed changes.
* *Note*: Retest period not applicable for biological/immunological active substance.	

B.I.e) Design space

B.I.e.1 Introduction of a new design space or extension of an approved design space for the active substance, concerning:		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	One unit operation in the manufacturing process of the active substance including the resulting in-process controls and/or test procedures		1, 2, 3	II
b)	Test procedures for starting materials/reagents/ intermediates and/or the active substance		1, 2, 3	II
Documentation				
1.	The design space has been developed in accordance with the relevant European and international scientific guidelines. Results from product, process and analytical development studies (e.g. interaction of the different parameters forming the design space have to be studied, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the active substance has been achieved.			
2.	Description of the Design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.			
3.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

B.I.e.2 Introduction of a post approval change management protocol related to the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
		1, 2, 3	**II**
Documentation			
1. Detailed description for the proposed change.			
2. Change management protocol related to the active substance.			
3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

B.I.e.3 Deletion of an approved change management protocol related to the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	**1, 2**	**IAIN**
Conditions			
1. The deletion of the approved change management protocol related to the active substance is not a result of unexpected events or out of specification results during the implementation of the change (s) described in the protocol and does not have any effect on the already approved information in the dossier.			
Documentation			
1. Justification for the proposed deletion.			
2. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

B.I.e.4 Changes to an approved change management protocol		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Major changes to an approved change management protocol**			**II**
b)	**Minor changes to an approved change management protocol that do not change the strategy defined in the protocol**		**1**	**IB**
Documentation				

1.	Declaration that any change should be within the range of currently approved limits. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.

B.I.e.5 Implementation of changes foreseen in an approved change management protocol		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**The implementation of the change requires no further supportive data**	**1**	**1, 2, 4**	**IAIN**
b)	**The implementation of the change requires further supportive data**		**1, 2, 3, 4**	**IB**
c)	**Implementation of a change for a biological/immunological medicinal product**		**1, 2, 3, 4, 5**	**IB**
Conditions				
1.	The proposed change has been performed fully in line with the approved change management protocol.			
Documentation				
1.	Reference to the approved change management protocol.			
2.	Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.			
3.	Outcomes of trials conducted in accordance with the approved protocol for handling changes.			
4.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
5.	Copy of approved specifications of the active substance			

B.II. FINISHED PRODUCT

B.II.a) Description and composition

B.II.a.1 Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking.		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Changes in imprints, bossing or other markings**	**1, 2, 3, 4**	**1, 2**	**IAIN**
b)	**Changes in scoring/break lines intended to divide into equal doses**		**1, 2, 3**	**IB**
Conditions				
1.	Finished product release and end of shelf life specifications have not been changed (except for appearance).			
2.	Any ink must comply with the relevant pharmaceutical legislation.			
3.	The scoring/break lines are not intended to divide into equal doses.			
4.	Any product markings used to differentiate strengths should not be completely deleted.			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a detailed drawing or written description of the current and new appearance, and including revised product information as appropriate.			
2.	Samples of the finished product where applicable (see NTA, Requirements for samples in the Member States).			
3	Results of the appropriate Ph. Eur tests demonstrating equivalence in characteristics/correct dosing.			

B.II.a.2 Change in the shape or dimensions of the pharmaceutical form		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Immediate release tablets, capsules, suppositories and pessaries**	**1, 2, 3, 4**	**1, 4**	**IAIN**
b)	**Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses**		**1, 2, 3, 4, 5**	**IB**
c)	**Addition of a new kit for a radiopharmaceutical preparation with another fill volume**			**II**
Conditions				

1.	If appropriate, the dissolution profile of the reformulated product is comparable to the current one. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the new product compared to the current one.
2.	Release and end of shelf-life specifications of the product have not been changed (except for dimensions).
3.	The qualitative or quantitative composition and mean mass remain unchanged.
4.	The change does not relate to a scored tablet that is intended to be divided into equal doses.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a detailed drawing of the current and proposed situation, and including revised product information as appropriate.
2.	Comparative dissolution data on at least one pilot batch of the current and proposed dimensions (no significant differences regarding comparability see the relevant guidance on Bioavailability of medicinal products for human use). For herbal medicinal product comparative disintegration data may be acceptable.
3.	Justification for not submitting a new bioequivalence study according to the relevant (Human or Veterinary) guidance on Bioavailability of medicinal products for human use.
4.	Medicinal product samples, when required (see NTA, Requirements for samples in Romania).
5.	Results of the appropriate Ph. Eur tests demonstrating equivalence in characteristics/correct dosing.
	Note: For B.II.a.2.c Applicants are reminded that any change to the "strength" of the medicinal product requires the submission of an Extension application.

B.II.a.3 Changes in the composition (excipients) of the finished product		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Changes in components of the flavouring or colouring system**			
	1. Addition, deletion or replacement	**1, 2, 3, 4, 5, 6, 7, 9, 11**	**1, 2, 4, 5, 6**	**IAIN**
	2. Increase or reduction	**1, 2, 3, 4, 11**	**1, 2, 4**	**IA**
b)	**Other excipients**			
	1. Any minor adjustment of the quantitative composition of the finished product with respect to excipients	**1, 2, 4, 8, 9, 10**	**1, 2, 7**	**IA**
	2. Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product			**II**
	3. Change that relates to a biological/immunological product			**II**
	4. Any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk			**II**
	5. Change that is supported by a bioequivalence study			**II**
	6. Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level		**1, 3, 4, 5, 6, 7, 8, 9, 10**	**IB**
Conditions				
1.	No change in functional characteristics of the pharmaceutical form e.g. disintegration time, dissolution profile.			
2.	Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the finished product formulation.			
3.	The finished product specification has only been updated in respect of appearance/odour/taste and if relevant, deletion of an identification test.			
4.	Stability studies have been started under ICH conditions (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant (at time of implementation for Type IAs and at time of notification for Type IBs) and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalised and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specification at the end of the			

	approved shelf life (with proposed action). In addition, where relevant, photo-stability testing should be performed.
5.	Any new proposed components must comply with the relevant Directives (e.g. Directive 94/36/EC and 2008/128/EC for colours for use in foodstuff and Directive 88/388/EEC for flavours).
6.	No new component includes the use of materials of human or animal origin for which assessment is required of viral safety data or compliance with the current *Note For Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products*.
7.	Where applicable, the change does not affect the differentiation between strengths and does not have a negative impact on taste acceptability for paediatric formulations.
8.	The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the current one (no significant differences regarding comparability, see the relevant guidance on Bioavailability of medicinal products for human use). For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the current one.
9.	The change is not the result of stability issues and/or should not result in potential safety concerns i.e. differentiation between strengths.
10.	The product concerned is not a biological/immunological medicinal product.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including identification method for any new colorant, where relevant, and including revised product information as appropriate.
2.	A declaration that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
3.	The results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
4.	Sample of the new product, where applicable (see NTA, Requirements for samples in Romania).
5.	Either a Ph. Eur. Certificate of Suitability for any new component of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by the competent authority and shown to comply with the scope of the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products*. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.
6.	Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate.
7	Justification for the change/choice of excipients etc. must be given by appropriate development pharmaceutics (including stability aspects and antimicrobial preservation where appropriate).
8.	For solid dosage forms, comparative dissolution profile data of at least two pilot scale batches of the finished product in the new and old composition. For herbal medicinal products, comparative disintegration data may be acceptable.
9.	Justification for not submitting a new bioequivalence study according to the current *Note for Guidance on The Investigation of Bioavailability and Bioequivalence.*

B.II.a.4 Change in coating weight of oral dosage forms or change in weight of capsule shells	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Solid oral pharmaceutical forms	**1, 2, 3, 4**	**1, 2**	**IA**
b) Gastro-resistant, modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism			**II**
Conditions			

1.	The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the current one. For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the current one.
2.	The coating is not a critical factor for the release mechanism.
3.	The finished product specification has only been updated in respect of weight and dimensions, if applicable.
4.	Stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant at the time of implementation and assurance that these studies will be finalised; data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
2.	A declaration that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). In addition, where relevant, photo-stability testing should be performed.

B.II.a.5 Change in concentration of a single-dose, total use parenteral product, where the amount of active substance per unit dose (i.e. the strength) remains the same	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
			II

B.II.a.6 Deletion of the solvent / diluent container from the pack	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
		1, 2	**IB**
Documentation			
1	Justification for the deletion, including a statement regarding alternative means to obtain the solvent / diluent as required for the safe and effective use of the medicinal product.		
2.	Revised product information.		

B.II.b) Manufacture

B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Secondary packaging site**	**1, 2**	**1,3, 8**	**IAIN**
b)	**Primary packaging site**	**1, 2, 3, 4, 5**	**1, 2, 3, 4, 8, 9**	**IAIN**
c)	**Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/ immunological medicinal products, or for pharmaceutical forms manufactured by complex manufacturing processes**			**II**
d)	**Site which requires an initial or product specific inspection**			**II**
e)	**Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products**		**1, 2, 3, 4, 5, 6, 7, 8, 9**	**IB**
f)	**Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products**		**1, 2, 3, 4, 5, 6, 7, 8**	**IB**
Conditions				
1.	Satisfactory inspection in the last three years by an inspection service of one of the Member States of the EU/EEA or of a country where an operational Good Manufacturing Practice (GMP) mutual recognition agreement (MRA) exists between the country concerned and the EU.			

2.	Site appropriately authorised (to manufacture the pharmaceutical form or product concerned).
3.	Product concerned is not a sterile product
4.	Where relevant, for instance for suspensions and emulsions, validation scheme is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches.
5.	Product concerned is not a biological/immunological medicinal product.
Documentation	
1.	Proof that the proposed site is appropriately authorised for the pharmaceutical form or product concerned, i.e.: For a manufacturing site within the EU/EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMP database will suffice; For a manufacturing site outside the EU/EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority; For a manufacturing site outside the EU/EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EU/EEA. A reference to the EudraGMP database will suffice.
2.	Where relevant, the batch numbers, corresponding batch size and the manufacturing date of batches (≥ 3) used in the validation study should be indicated and the validation data presented, or validation protocol (scheme) to be submitted.
3.	The variation application form should clearly outline the "present" and "proposed" finished product manufacturers as listed in section 2.5 of the application form.
4.	Copy of approved release and end-of-shelf life specifications if relevant.
5.	Batch analysis data on one production batch and two pilot-scale batches simulating the production process (or two production batches) and comparative data on the last three batches from the previous site; batch data on the next two production batches should be available on request or reported if outside specifications (with proposed action).
6.	For semisolid and liquid formulations in which the active substance is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology or any other appropriate imaging technique.
7.	i) If the new manufacturing site uses the active substance as a starting material – A declaration by the Qualified Person (QP) at the site responsible for batch release that the active substance is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union. ii) In addition, if the new manufacturing site is located within the EU/EEA and uses the active substance as a starting material – A declaration by the Qualified Person (QP) of the new manufacturing site that the active substance used is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union.
8.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
9.	If the manufacturing site and the primary packaging site are different, conditions of transport and bulk storage should be specified and validated.
Notes	
	In case of a change in or a new manufacturing site in a country outside the EU/EEA without an operational GMP mutual recognition agreement with the EU, marketing authorisation holders are advised to consult the relevant competent authorities first before making the submission of the notification and to provide information about any previous EU/EEA inspection in the last 2-3 years and/or any planned EU/EEA inspection(s) including inspection dates, product category inspected, Supervisory Authority and other relevant information. This will facilitate the arrangement for a GMP inspection by an inspection service of one of the Member States if needed. **QP Declarations in relation to active substances** Manufacturing authorisation holders are obliged to only use as starting materials active substances that have been manufactured in accordance with GMP so a declaration is expected from each of the manufacturing authorisation holders that use the active substance as a starting material. In addition, as the QP responsible for batch certification takes overall responsibility for each batch, a further declaration from the QP responsible for batch certification is expected when the batch release site is a different site from the above.

In many cases only one manufacturing authorisation holder is involved and therefore only one declaration will be required. However, when more than one manufacturing authorisation holder is involved rather than provide multiple declarations it may be acceptable to provide a single declaration signed by one QP. This will be accepted provided that:

The declaration makes it clear that it is signed on behalf of all the involved QPs.

The arrangements are underpinned by a technical agreement as described in Chapter 7 of the GMP Guide and the QP providing the declaration is the one identified in the agreement as taking specific responsibility for the GMP compliance of the active substance manufacturer(s). *Note:* These arrangements are subject to inspection by the competent authorities.

Applicants are reminded that a Qualified Person is at the disposal of a manufacturing authorisation holder according to Article 749 (1) d) of the Law transposing Article 41 of Directive 2001/83/EC, located in the EU/EEA. Therefore declarations from personnel employed by manufacturers in third countries, including those located within MRA partner countries are not acceptable.

According to Article 755 (1) of the Law, transposing Article 46a of Directive 2001/83/EC, the manufacture of active substances used as starting materials includes complete or partial manufacture, import, dividing up, packaging or presentation prior to its incorporation into a medicinal product, including re-packaging or re-labelling as carried out by a distributor.

A declaration is not required for blood or blood components they are subject to the requirements of Directive 2002/98/EC.

B.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Replacement or addition of a site where batch control/testing takes place**	**2, 3, 4, 5**	**1, 2, 5**	**IA**
b)	**Replacement or addition of a site where batch control/testing takes place for a biological/immunological product and any of the test methods performed at the site is a biological/immunological method**			**II**
c)	**Replacement or addition of a manufacturer responsible for importation and/or batch release**			
	1. Not including batch control/testing	**1, 2.5**	**1, 2, 3, 4, 5**	**IAIN**
	2. Including batch control/testing	**1, 2, 3, 4, 5**	**1, 2, 3, 4, 5**	**IAIN**
	3. Including batch control/testing for a biological/immunological product and any of the test methods performed at that site is a biological / immunological / immunochemical method			**II**

Conditions

1. The manufacturer responsible for batch release must be located within the EU/EEA. At least one batch release site remains within the EU/EEA that is able to certify the product testing for the purpose of batch release within the EU/EEA.
2. The site is appropriately authorised.
3. The product is not a biological/immunological medicinal product.
4. Method transfer from the old to the new site or new test laboratory has been successfully completed.
5. At least one batch control/testing site remains within the EU/EEA or in a country where an operational and suitably scoped GMP mutual recognition agreement (MRA) exists between the country concerned and the EU, that is able to carry out product testing for the purpose of batch release within the EU/EEA.

Documentation

1. For a site within the EU/EEA: Attach copy of manufacturing authorisation(s) or where no manufacturing authorisation exists a certificate of GMP compliance issued within the last 3 years by the relevant competent authority.

   For a manufacturing site outside the EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate, issued within the last 3 years

	by the relevant competent authority. Where no such agreement exists a GMP certificate issued within the last 3 years by a EU/EEA competent authority.
2.	The variation application form should clearly outline the "present" and "proposed" finished product manufacturers, importer, batch control/testing and batch release sites as listed in section 2.5 of the application form for marketing authorisation.
3.	A declaration by the Qualified Person (QP) responsible for batch certification stating that the active substance manufacturer(s) referred to in the marketing authorisation operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances - see the note under variation no. B.II.b.1.
4	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD), including revised product information as appropriate.

B.II.b.3 Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Minor change in the manufacturing process**	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 3, 4, 5, 6, 7, 8**	**IA**
b)	**Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product**			**II**
c)	**The product is a biological/immunological medicinal product and the change requires an assessment of comparability**			**II**
d)	**Introduction of a non-standard terminal 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**		**1, 2, 4, 6, 7,8**	**IB**
1.	No change in qualitative and quantitative impurity profile or in physico-chemical properties.			
2.	Either the change relates to: - an immediate release solid oral dosage form / oral solution and the medicinal product concerned is not a biological /immunological or herbal medicinal product; or to process parameter(s) that, in the context of a previous assessment, have been considered to have no impact on the quality of the finished product (regardless of the type of product and/or dosage form).			
3.	The manufacturing principle including the single manufacturing steps remain the same, e.g. processing intermediates and there are no changes to any manufacturing solvent used in the process.			
4	The already authorised product should undergo relevant in-process controls and does not require changes (limit extension or deletion).			
5.	The specifications of the finished product or intermediates are unchanged.			
6.	The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.			
7.	Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batch and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a direct comparison of the present process and the new process.			
2.	For semi-solid and liquid products in which the active substance is present in non-dissolved form: appropriate validation of the change including microscopic imaging of particles to check for visible changes in morphology; comparative size distribution data by an appropriate method.			
3.	For solid dosage forms: dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside specification (with proposed action). For herbal medicinal products, comparative disintegration data may be acceptable.			
4.	Justification for not submitting a new bioequivalence study according to the relevant guidance on Bioavailability (of medicinal products for human use).			
5.	For changes to process parameter(s) that have been considered to have no impact on the quality of the finished product, declaration to this effect reached in the context of the previously approved risk assessment.			

6.	Copy of approved release and end-of-shelf life specifications.
7.	Batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured to both the currently approved and the proposed process. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).
8.	Declaration that relevant stability studies have been started under ICH conditions, as appropriate, (with indication of the batch numbers concerned) and relevant stability parameters have been assessed in at least one pilot scale or industrial scale batch and at least three months satisfactory stability data are at the disposal of the applicant at time of notification and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalised and that the data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

B.II.b.4 Change in the batch size (including batch size ranges) of the finished product		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Up to 10-fold compared to the originally approved batch size**	**1, 2, 3, 4, 5, 7**	**1, 4**	**IA**
b)	**Downscaling down to 10-fold**	**1, 2, 3, 4, 5, 6**	**1, 4**	**IA**
c)	**The change requires assessment of the comparability of a biological/immunological medicinal product or the change in batch size requires a new bioequivalence study**			**II**
d)	**The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes**			**II**
e)	**More than 10-fold increase compared to the originally approved batch size for immediate release (oral) pharmaceutical forms**		**1, 2, 3, 4, 5, 6**	**IB**
f)	**The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)**		**1, 2, 3, 4, 5, 6**	**IB**

	Conditions
1.	The change does not affect reproducibility and/or consistency of the product.
2.	The change relates to conventional immediate release oral pharmaceutical forms or to non-sterile liquid based pharmaceutical forms.
3.	Any changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch-size, e.g. use of different sized equipment.
4.	Validation scheme is available or validation of the manufacture has been successfully carried out according to the current protocol with at least three batches at the proposed new batch size in accordance with the relevant guidelines.
5.	The product concerned is not a biological/immunological medicinal product.
6.	The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
7.	The batch size is within the 10-fold range of the batch size foreseen when the marketing authorisation was granted or following a subsequent change not agreed as a Type IA variation.
	Documentation
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
2.	Batch analysis data (in a comparative tabulated format) on a minimum of one production batch manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the MAH if outside specifications (with proposed action).
3.	Copy of approved release and end-of-shelf life specifications.
4.	Where relevant the batch numbers, corresponding batch size and the manufacturing date of batches (≥3) used in the validation study should be indicated or validation protocol (scheme) be submitted.
5.	The validation results should be provided.
6.	The results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least one pilot or industrial scale batch, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). For biologicals/immunologicals: a declaration that an assessment of comparability is not required.

B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product		Conditions to be fulfilled	Documentation to be supplied	Variation type
a)	**Tightening of in-process limits**	**1, 2, 3, 4**	**1, 2**	**IA**
b)	**Addition of new tests and limits**	**1, 2, 5, 6**	**1, 2, 3, 4, 5, 7**	**IA**
c)	**Deletion of a non-significant in-process test**	**1, 2, 7**	**1, 2, 6**	**IA**
d)	**Deletion of an in-process test which may have a significant effect on the overall quality of the finished product**			**II**
e)	**Widening of the approved IPC limits, which may have a significant effect on the overall quality of the finished product**			**II**
f)	**Addition or replacement of an in-process test as a result of a safety quality issue**		**1, 2, 3, 4, 5, 7**	**IB**

Conditions	
1.	The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2.	The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.
3.	Any change should be within the range of currently approved limits.
4.	The test procedure remains the same, or changes in the test procedure are minor.
5.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6.	The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).
7.	The in-process test does not concern the control of a critical parameter. e.g.: assay, impurities (unless a particular solvent is definitely not used in the manufacture) any critical physical characteristics (particle size, bulk, tapped density…) identity test (unless there is a suitable alternative control already present) microbiological control (unless not required for the particular dosage form)
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
2.	Comparative table of current and proposed in-process tests and limits.
3.	Details of any new analytical method and validation data, where relevant.
4.	Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters.
5.	Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch manufactured using the current and new in-process tests. For herbal medicinal products, comparative disintegration data may be acceptable.
6	Justification/risk assessment showing that the in-process test is non-significant or that it is obsolete.
7.	Justification of the new in-process test and limits.

B.II.c) Control of excipients

B.II.c.1 Change in the specification parameters and/or limits of an excipient		Conditions to be fulfilled	Documentation to be supplied	Variation type
a)	**Tightening of specification limits**	**1, 2, 3, 4**	**1, 2**	**IA**
b)	**Addition of a new specification parameter (e.g. deletion of an obsolete parameter)**	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 6, 8**	**IA**
c)	**Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)**	**1, 2, 8**	**1, 2, 7**	**IA**
d)	**Change outside the approved specifications limits range**			**II**

e)	**Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product**			**II**
f)	**Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method, as a result of a safety or quality issue**		**1, 2, 3, 4, 5, 6, 8**	**IB**
g)	**Where there is no monograph in the 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**		**1, 2, 3, 4, 5, 6, 8**	**IB**
Conditions				
1.	The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).			
2.	The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.			
3.	Any change should be within the range of currently approved limits.			
4.	The test procedure remains the same, or changes in the test procedure are minor.			
5.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
6.	The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).			
7.	The change does not concern a genotoxic impurity.			
8.	The specification parameter does not concern the control of a critical parameter. e.g.: impurities (unless a particular solvent is definitely not used in the manufacture of the excipient) any critical physical characteristics (particle size, bulk, tapped density…) identity test (unless there is a suitable alternative control already present) microbiological control (unless not required for the particular dosage form)			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
2.	Comparative table of current and proposed specifications.			
3.	Details of any new analytical method and validation data, where relevant.			
4.	Batch analysis data on two production batches (3 production batches for biological excipients) of the excipient for all specification parameters.			
5.	Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the excipient complying with the current and proposed specification. For herbal medicinal products comparative disintegration data may be acceptable.			
6.	Justification for not submitting a new bioequivalence study according to the relevant (Human, Veterinary) Guideline on *Bioavailability*, if appropriate.			
7.	Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.			
8.	Justification of the new specification parameter and the limits.			

B.II.c.2 Change in test procedure for an excipient		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Minor changes to an approved test procedure**	**1, 2, 3, 4**	**1, 2**	**IA**
b)	**Deletion of a test procedure if an alternative test procedure is already authorised**	**5**	**1**	**IA**
c)	**Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biochemical reagent**			**II**
d)	**Other changes to a test procedure (including replacement or addition)**		**1, 2**	**IB**
Conditions				
1.	Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.			

2.	There have been no changes of the total impurity limits; no new unqualified impurities are detected.
3.	The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
4.	The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).
5.	An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA(IN) notification.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).
2.	Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.II.c.3 Change in source of an excipient or reagent with TSE risk	**Conditions to be fulfilled**	**Documentation to be supplied**	**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**	**1**	**1**	**IA**
2. **For excipients or reagents used in the manufacture of a biological / immunological active substance or in a biological / immunological medicinal product**		**1, 2**	**IB**
b) **Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by a TSE certificate of suitability**			**II**
Conditions			
1. Excipient and finished product release and end of shelf life specifications remain the same.			
Documentation			
1. Declaration from the manufacturer or the marketing authorisation holder of the material that it is purely of vegetable or synthetic origin.			
2. Study of equivalence of the materials and the impact on production of the final material and impact on behaviour (e.g. Dissolution characteristics) of the finished product.			

B.II.c.4 Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier) or a novel excipient	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Minor change in synthesis or recovery of a non-pharmacopoeial excipient or a novel excipient	**1, 2**	**1, 2, 3, 4**	**IA**
b) The specifications are affected or there is a change in 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**
Conditions			
1. The synthetic route and specifications are identical and there is no change in qualitative and quantitative impurity profile (excluding residual solvents, provided they are controlled in accordance with ICH limits), or in physico-chemical properties.			
2. Adjuvants are excluded.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
2. Batch analysis data (in a comparative tabulated format) of at least two batches (minimum pilot scale) of the excipient manufactured according to the old and the new process.			

3.	Where appropriate, comparative dissolution profile data for the finished product of at least two batches (minimum pilot scale). For herbal medicinal products, comparative disintegration data may be acceptable.
4.	Copy of approved and new (if applicable) specifications of the excipient.

B.II.d) Control of finished product

B.II.d.1 Change in the specification parameters and/or limits of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Tightening of specification limits for medicinal products subject to batch release performed by the official competent authority	**1, 2, 3, 4**	**1, 2**	**IAIN**
c) Addition of a new specification parameter (e.g. deletion of an obsolete parameter)	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 7**	**IA**
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material)	**1, 2, 9**	**1, 2, 6**	**IA**
e) Change outside the approved specifications limits range			**II**
f) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product			**II**
g) Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method as a result of a safety or quality issue		**1, 2, 3, 4, 5, 7**	**IB**
h) **Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur for the finished product***	**1, 2, 3, 4, 7, 8**	**1, 2**	**IAIN**
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)**	**1, 2,10**	**1, 2, 4**	**IA**

Conditions	
1.	The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure), unless the supporting documentation has been already assessed and approved within another procedure.
2.	The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.
3.	Any change should be within the range of currently approved limits.
4.	The test procedure remains the same, or changes in the test procedure are minor.
5.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6.	The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance.
7.	The change does not concern any impurities (including genotoxic) or dissolution.
8.	The change concerns the updating of the microbial control limits to be in line with the current Pharmacopoeia, and the currently registered microbial control limits (present situation) are in line with the pre January 2008 (non harmonised) situation and does not include any additional specified controls over the Pharmacopoeia requirements for the particular dosage form and the proposed controls are in line with the harmonised monograph.
9.	The specification parameter or proposal for the specific dosage form does not concern a critical parameter for example: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the finished product) any critical physical characteristics (hardness or friability for uncoated tablets, dimensions…)

	a test that is required for the particular dosage form in accordance with the general notices of the Ph. Eur.; any request for skip testing.
10	The proposed control is fully in line with the Table 2.9.40.-1 of Ph. Eur. 2.9.40 monograph, and does not include the alternative proposal for testing uniformity of dosage units by Mass Variation instead of Content Uniformity when the latter is specified in Table 2.9.40.-1.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
2.	Comparative table of current and proposed specifications.
3.	Details of any new analytical method and validation data, where relevant.
4.	Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters
5.	Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.
6	Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.
7.	Justification of the new specification parameter and the limits
* Note: There is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that reference is made to the 'current edition' in the dossier of an authorised medicinal product. This variation therefore applies to cases where no reference to the updated monograph of the pharmacopoeia was contained in the technical dossier and the variation is made to make reference to the updated version.	

B.II.d.2 Change in test procedure for the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Minor changes to an approved test procedure	**1, 2, 3, 4,**	**1,2**	**IA**
b) Deletion of a test procedure if an alternative method is already authorised	**4**	**1**	**IA**
c) Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biochemical reagent or replacement of a reference biological preparation and which is not a part of an approved protocol			**II**
d) Other changes to a test procedure (including replacement or addition)		**1, 2**	**IB**
e) Update of the test procedure to comply with the updated general monograph in the Ph. Eur.	**2, 3, 4, 5**	**1**	**IA**
f) To reflect compliance with the Ph.Eur. and remove reference to the outdated internal test method and test method number*	**2, 3, 4, 5**	**1**	**IA**
Conditions			
1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.			
2. There have been no changes of the total impurity limits; no new unqualified impurities are detected			
3. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method);			
4. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).			
5. The registered test procedure already refers to the general monograph of the Ph. Eur. and any changes are minor in nature and require update of the technical dossier.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).			

2.	Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.
* Note: There is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia in the case that reference is made to the 'current edition' in the dossier of an authorised medicinal product.	

B.II.d.3 Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
			II

B.II.e) Container closure system

B.II.e.1 Change in immediate packaging of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Qualitative and quantitative composition			
1. Solid pharmaceutical forms	**1, 2, 3**	**1, 2, 3, 4, 6**	**IA**
2. Semi-solid and non-sterile liqui pharmaceutical forms		**1, 2, 3, 5, 6**	**IB**
3. Sterile medicinal products and biological/ immunological medicinal products.			**II**
4. The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.			**II**
b) **Change in type of container or addition of a new container**			
1. Solid, semi-solid and non-sterile liquid pharmaceutical forms		**1, 2, 3, 5, 6, 7**	**IB**
2. Sterile medicinal products and biological/ immunological medicinal products			**II**
3. Deletion of an immediate packaging container that does not lead to the complete deletion of a strength or pharmaceutical form	4	**1, 8**	**IA**

Conditions	
1.	The change only concerns the same packaging/container type (e.g. blister to blister).
2.	The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.
3.	Relevant stability studies have been started under ICH conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging e.g. thicker blister packaging, the three months' stability data do not yet have to be available. These studies must be finalised and the data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
4.	The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.
2.	Appropriate data on the new packaging (comparative data on permeability e.g. for O_2, CO_2 moisture).

3.	Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeial requirements or legislation of the Union on plastic material and objects in contact with foodstuffs.
4.	A declaration that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
5.	The results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
6.	Comparative table of the current and proposed immediate packaging specifications, if applicable.
7.	Samples of the new container/closure where applicable (see NTA, Requirements for samples in the Member States/EMA).
8.	Declaration that the remaining pack-size(s) is/are consistent with the dosage regimen and duration of treatment and adequate for the dosing instructions as approved in the summary of product characteristics.
Note: For B.II.e.1.b) applicants are reminded that any change which results in a "new pharmaceutical form" requires the submission of an Extension application.	

B.II.e.2 Change in the specification parameters and/or limits of the immediate packaging of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5**	**1, 2, 3, 4, 6**	**IA**
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**1, 2**	**1, 2, 5**	**IA**
d) Addition or replacement of a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4, 6**	**IB**
Conditions			
1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).			
2. The change does not result from unexpected events arising during manufacture			
3. Any change should be within the range of currently approved limits.			
4. The test procedure remains the same, or changes in the test procedure are minor.			
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
2. Comparative table of current and proposed specifications.			
3. Details of any new analytical method and validation data, where relevant.			
4. Batch analysis data on two batches of the immediate packaging for all specification parameters.			
5. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.			
6. Justification of the new specification parameter and the limits.			

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

b)	**Other changes to a test procedure (including replacement or addition)**	**1, 3, 4**	**1, 2**	**IA**
c)	**Deletion of a test procedure if an alternative test procedure is already authorised**	**5**	**1**	**IA**
Conditions				
1.	Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.			
2.	The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).			
3.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
4.	The active substance/ finished product is not biological/immunological.			
5.	An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA(IN) notification.			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a description of the analytical methodology, a summary of validation data.			
2.	Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.			

B.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging)		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a)	**Non-sterile medicinal products**	**1, 2, 3**	**1, 2, 4**	**IA**
b)	**The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product**			**II**
c)	**Sterile medicinal products**		**1, 2, 3, 4**	**IB**
Conditions				
1.	No change in the qualitative or quantitative composition of the container.			
2.	The change does not concern a fundamental part of the packaging material, which affects the delivery**,** use, safety or stability of the finished product.			
3.	In case of a change in the headspace or a change in the surface/volume ratio, stability studies in accordance with the relevant guidelines have been started and relevant stability parameters have been assessed in at least two pilot scale (three for biological/immunological medicinal products) or industrial scale batches and at least three months (six months for biological/immunological medicinal products) stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including description, detailed drawing and composition of the container or closure material, and including revised product information as appropriate.			
2.	Samples of the new container/closure system, where applicable (see NTA, Requirements for samples in Romania).			
3.	Re-validation studies have been performed in case of sterile products terminally sterilised. The batch numbers of the batches used in the re-validation studies should be indicated, where applicable.			
4.	In case of a change in the headspace or a change in the surface/volume ratio, a declaration that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation for a Type IA notification and time of submission of a Type IB notification, and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the NAMMD if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).			

B.II.e.5 Change in pack size of the finished product	Conditions to be fulfilled	Documentation to be supplied	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	**1, 2**	**1, 3**	**IAIN**
2. Change outside the range of the currently approved pack sizes		**1, 2, 3**	**IB**
b) Deletion of pack size(s)	**3**	**1, 2**	**IA**
c) Change in the fill weight/fill volume of sterile 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		**1, 2, 3**	**IB**
Conditions			
1. New pack size should be consistent with the posology and treatment duration as approved in the Summary of Product Characteristics.			
2. The primary packaging material remains the same.			
3. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the Summary of Product Characteristics.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format) including revised product information as appropriate.			
2. Justification for the new/remaining pack-size, showing that the new/remaining size is/are consistent with the dosage regimen and duration of treatment as approved in the summary of product characteristics			
3. Declaration that stability studies will be conducted in accordance with the relevant guidelines for products where stability parameters could be affected. Data to be reported only if outside specifications (with proposed action).			
Note: For B.II.e.5.c) and d), applicants are reminded that any changes to the 'strength' of the medicinal product require the submission of an Extension application.			

B.II.e.6 Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used))	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) Change that affects the product information	**1**	**1**	**IAIN**
b) Change that does not affect the product information	**1**	**1**	**IA**
Conditions			
1. The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including revised product information as appropriate.			

B.II.e.7 Change in supplier of packaging components or devices (when mentioned in the dossier)	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) Deletion of a supplier	**1**	**1**	**IA**
b) Replacement or addition of a supplier	**1, 2, 3, 4**	**1, 2, 3**	**IA**
c) Any change to suppliers of spacer devices for metered dose inhalers			**II**
Conditions			

1.	No deletion of packaging component or device.
2.	The qualitative and quantitative composition of the packaging components/device and design specifications remain the same.
3.	The specifications and quality control method are at least equivalent.
4.	The sterilisation method and conditions remain the same, if applicable.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
2.	For devices for medicinal products for human use, proof of CE marking.
3.	Comparative table of current and proposed specifications, if applicable.

B.II.f) Stability

B.II.f.1 Change in the shelf-life or storage conditions of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Reduction of the shelf life of the finished product			
1. As packaged for sale	**1**	**1, 2, 3**	**IAIN**
2. After first opening	**1**	**1, 2, 3**	**IAIN**
3. After dilution or reconstitution	**1**	**1, 2, 3**	**IAIN**
b) Extension of the shelf life of the finished product			
1. As packaged for sale (supported by real time data)		**1, 2, 3**	**IB**
2. After first opening (supported by real time data)		**1, 2, 3**	**IB**
3. After dilution or reconstitution (supported by real time data)		**1, 2, 3**	**IB**
4. Extension of the shelf-life based on extrapolation of stability data not in accordance with ICH guidelines*			**II**
5. Extension of the shelf-life of a biological/ immunological medicinal product in accordance with an approved stability protocol.		**1, 2, 3**	**IB**
c) **Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol**			**II**
d) **Change in storage conditions of the finished product or the diluted/reconstituted product**		**1, 2, 3**	**IB**
e) **Change to an approved stability protocol**	**1, 2**	**1, 4**	**IA**

Conditions	
1.	The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
2.	The change does not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format). This must contain results of appropriate real time stability studies (covering the entire shelf life) conducted in accordance with the relevant stability guidelines on at least two pilot scale batches[1] of the finished product in the authorised packaging material and/or after first opening or reconstitution, as appropriate; where applicable, results of appropriate microbiological testing should be included. [1]Pilot scale batches can be accepted with a commitment to verify the shelf life on production scale batches.
2.	Revised product information

3. Copy of approved end of shelf life finished product specification and where applicable, specifications after dilution/reconstitution or first opening.
4. Justification for the proposed change(s).
*Note: extrapolation not applicable for biological/immunological medicinal product

B.II.g) **Design Space and post approval change management protocol**

B.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product, concerning:	**Conditions to be fulfilled**	**Documentation to be supplied**	**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		**1, 2, 3**	**II**
b) Test procedures for excipients / intermediates and/or the finished product.		**1, 2, 3**	**II**
Documentation			
1. Results from product and process development studies (including risk assessment and multivariate studies, as appropriate) demonstrating that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the finished product has been achieved.			
2. Description of the design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.			
3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

B.II.g.2 Introduction of a post approval change management protocol related to the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
		1, 2, 3	**II**
Documentation			
1. Detailed description for the proposed change.			
2. Change management protocol related to the finished product.			
3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

B.II.g.3 Deletion of an approved change management protocol related to the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	**1, 2**	**IAIN**
Conditions			
1. The deletion of the approved change management protocol related to the finish product is not a result of unexpected events or out of specification results during the implementation of the change (s) described in the protocol and does not have any effect on the already approved information in the dossier.			
Documentation			
1. Justification for the proposed deletion.			
2. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

B.II.g.4 Changes to an approved change management protocol	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Major changes to an approved change management protocol			**II**
b) Minor changes to an approved change management protocol that do not change the strategy defined in the protocol		**1**	**IB**
Documentation			

1.	Declaration that any change should be within the range of currently approved limits. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.

B.II.g.5 Implementation of changes foreseen in an approved change management protocol	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) The implementation of the change requires no further supportive data	**1**	**1, 2, 4**	**IAIN**
b) The implementation of the change requires further supportive data		**1, 2, 3, 4**	**IB**
c) Implementation of a change for a biological/immunological medicinal product		**1, 2, 3, 4, 5**	**IB**
Conditions			
1. The proposed change has been performed in full accordance with the approved chane management protocol, stating that the change must be immediately notified after enforcement.			
Documentation			
1. Reference to the approved change management protocol.			
2. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.			
3. Results of the studies performed in accordance with the approved change management protocol.			
4. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
5. Copy of approved specifications of the finished product.			

B.II.h Adventitious Agents Safety

B.II.h.1 Update to the "Adventitious Agents Safety Evaluation" information (section 3.2.A.2)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Studies related to manufacturing steps investigated for the first time for one or more adventitious agents			**II**
b) Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier			
1) with modification of risk assessment			**II**
2) without modification of risk assessment		**1, 2, 3**	**IB**
Documentation			
1. Amendment of the relevant section(s) of the dossiers including the introduction of the new studies to investigate the capability of manufacturing steps to inactivate/reduce adventitious agents.			
2. Justification that the studies do not modify the risk assessment.			
3. Amendment of product information (where applicable).			

B.III CEP/TSE/MONOGRAPHS

B.III.1 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: **For an active substance** **For a starting material/reagent/intermediate used in the manufacturing process of the active substance** **For an excipient**	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.			

	1.	New certificate from an already approved manufacturer	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA$_{IN}$**
	2.	Updated certificate from an already approved manufacturer	**1, 2, 3, 4, 8**	**1, 2, 3, 4, 5**	**IA**
	3.	New certificate from a new manufacturer (replacement or addition)	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA$_{IN}$**
	4.	Deletion of certificates (in case multiple certificates exist per material)	**10**	**3**	**IA**
	5.	New certificate for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free		**1, 2, 3, 4, 5, 6**	**IB**
b)	**European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient**				
	1.	New certificate for an active substance from a new or an already approved manufacturer	**3, 5, 6, 11**	**1, 2, 3, 4, 5**	**IA$_{IN}$**
	2.	New certificate for a starting material/reagent/ intermediate/or excipient from a new or an already approved manufacturer	**3, 6, 9**	**1, 2, 3, 4, 5**	**IA**
	3.	Updated certificate from an already approved manufacturer	**7, 9**	**1, 2, 3, 4, 5**	**IA**
	4.	Deletion of certificates (in case multiple certificates exist per material)	**10**	**3**	**IA**
	5.	New/updated certificate from an already-approved/new manufacturer using materials of human or animal origin for which an assessment of the risk with respect to potential contamination with adventitious agents is required			II

Conditions	
1.	The finished product release and end of shelf life specifications remain the same.
2.	Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH) and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3.	The manufacturing process of the active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
4.	For active substance only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier.
5.	The active substance/starting material/reagent/intermediate/excipient is not sterile.
6.	The substance is not included in a veterinary medicinal product for use in animal species susceptible to TSE
7.	For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.
8.	If Gelatine manufactured from bones is to be used in a medicinal product for parenteral use, it should **only** be manufactured in compliance with the relevant country requirements.
9.	At least one manufacturer for the same substance remains in the dossier.
10.	If the active substance is a not a sterile substance but is to be used in a sterile medicinal product then according to the CEP it must not use water during the last steps of the synthesis or if it does the active substance must also be claimed to be free from bacterial endotoxins.
Documentation	
1.	Copy of the current (updated) Ph. Eur. Certificate of Suitability.

2.	In case of an addition of a manufacturing site, the variation application form should clearly outline the "present" (approved under the marketing authorisation or following a variation) and "proposed" manufacturers.
3.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
4.	Where applicable, a document providing information of any materials falling within the scope of the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* including those which are used in the manufacture of the active substance/ excipient. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).
5.	Where applicable, for active substance, a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the QP of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances - see the note under variation no. B.II.b.1. The manufacture of intermediates also require a QP declaration, while as far as any updates to certificates for active substances and intermediates are concerned, a QP declaration is only required if, compared to the previously registered version of the certificate, there is a change to the actual listed manufacturing sites.
6.	Suitable evidence to confirm compliance of the water used in the final steps of the synthesis of the active substance with the corresponding requirements on quality of water for pharmaceutical use.

B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State		**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation 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	**1, 2, 3, 4, 5**	**1, 2, 3, 4**	**IA$_{IN}$**
	2. Excipient/active substance starting material	**1, 2,4**	**1, 2, 3, 4**	**IA**
b)	**Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State**	**1, 2, 4, 5**	**1, 2, 3, 4**	**IA**
c)	**Change in specifications from a national pharmacopoeia of a Member State to the Ph. Eur.**	**1, 4, 5**	**1, 2, 3, 4**	**IA**

Conditions	
1.	The change is made exclusively to fully comply with the pharmacopoeia. All the tests in the specification need to correspond to the pharmacopoeial standard after the change, except any additional supplementary tests.
2.	Additional specifications to the pharmacopoeia for product specific properties are unchanged (e.g. particle size profiles, polymorphic form or e.g. bioassays, aggregates).
3.	No significant changes in qualitative and quantitative impurities profile unless the specifications are tightened
4.	Additional validation of a new or changed pharmacopoeial method is not required
5.	For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
2.	Comparative table of current and proposed specifications.
3.	Batch analysis data (in a comparative tabulated format) on two production batches of the relevant substance for all tests in the new specification and additionally, where appropriate, comparative

	dissolution profile data for the finished product on at least one pilot batch.. For herbal medicinal products, comparative disintegration data may be acceptable**.**
4.	Data to demonstrate the suitability of the monograph to control the substance, e.g. a comparison of the potential impurities with the transparency note of the monograph.
Note: There is no need to notify the NAMMD of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that reference is made to the 'current edition' in the dossier of an authorised medicinal product.	

B.IV Medical devices

B.IV.1 Change of a measuring or administration device	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Addition or replacement of a device which is not an integrated part of the primary packaging			
1. Device with CE marking	**1, 2, 3, 6, 7**	**1, 2, 4**	**IA$_{IN}$**
2. Device without CE marking for veterinary products only			
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	**4, 5**	**1, 5**	**IA$_{IN}$**
c) Addition or replacement of a device which is an integrated part of the primary packaging			**II**
Conditions			
1. The proposed measuring or administration device must accurately deliver the required dose for the product concerned in line with the approved posology and results of such studies should be available.			
2. The new device is compatible with the medicinal product.			
3. The change should not lead to substantial amendments of the product information.			
4. The medicinal product can still be accurately delivered.			
5. For veterinary medicinal products, the device is not crucial for the safety of the person administering the product.			
6. The medical device is not used as a solvent of the medicinal product.			
7. If a measuring function is intended the CE marking should cover the measuring function.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including description, detailed drawing and composition of the device material and supplier where appropriate, and including revised product information as appropriate.			
2. Proof of CE marking and if a measuring function is intended the proof of CE marking should also include the 4 digit notified body number.			
3. Data to demonstrate accuracy, precision and compatibility of the device.			
4. Samples of the new device where applicable (see NTA, Requirements for samples in Romania).			
5. Justification for the deletion of the device.			
Note: For B.IV.1.c), applicants are reminded that any change which results in a "new pharmaceutical form" requires the submission of an Extension application.			

B.V. Changes to a marketing authorisation resulting from other regulatory procedures

B.V.a) PMF/VAMF

B.V.a.1 Inclusion of a new, updated or amended Plasma Master File in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure)	**Conditions to be fulfilled**	**Documentation to be supplied**	**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		**1, 2, 3, 4**	**IB**
c) Inclusion of an updated/amended Plasma Master File when changes affect the properties of the finished product		**1, 2, 3, 4**	**IB**
d) Inclusion of an updated/amended Plasma Master File when changes do not affect the properties of the finished product	**1**	**1, 2, 3, 4**	**IA_{IN}**
Conditions			
1. The updated or amended Plasma Master File has been granted a certificate of compliance with legislation of the Union in accordance with Order of the Minister of Health no. 906/2006 transposing Annex I of Directive 2001/83/EC.			
Documentation			
1. Declaration that: - the PMF Certificate and Evaluation Report are fully applicable for the authorised product; - PMF holder has provided the PMF Certificate, Evaluation report and PMF dossier to the MAH (where the MAH is different to the PMF holder; the PMF Certificate and Evaluation Report replace the previous PMF documentation for this Marketing Authorisation.			
2. PMF Certificate and Evaluation Report.			
3. An expert statement outlining all the changes introduced with the certified PMF and evaluating their potential impact on the finished products including product specific risk assessments.			
4. The variation application form should clearly outline the "present" and "proposed" PMF EMA Certificate (code number) in the MA dossier. When applicable, the variation application form should clearly list also all the other PMFs to which the medicinal product refers even if they are not the subject of the application.			

B.V.a.2 Inclusion of a new, updated or amended Vaccine Antigen Master File in the marketing authorisation dossier of a medicinal product. (VAMF 2nd step procedure)	**Conditions to be fulfilled**	**Documentation to be supplied**	**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		**1, 2, 3, 4**	**IB**
c) Inclusion of an updated/amended Vaccine Antigen Master File, when changes do not affect the properties of the finished product	**1**	**1, 2, 3, 4**	**IA_{IN}**
Conditions			
1. The updated or amended Plasma Master File has been granted a certificate of compliance with legislation of the Union in accordance with Order of the Minister of Health no. 906/2006 transposing Annex I of Directive 2001/83/EC.			
Documentation			
1. Declaration that: - VAMF Certificate and Evaluation Report are fully applicable for the authorised product; - VAMF holder has submitted the VAMF Certificate, Evaluation report and VAMF dossier to the MAH (where the MAH is different to the VAMF holder); - the VAMF Certificate and Evaluation Report replace the previous VAMF documentation for this Marketing Authorisation.			
2. VAMF Certificate and Evaluation Report.			
3. An expert statement outlining all the changes introduced with the certified VAMF and evaluating their potential impact on the finished products including product specific risk assessments.			
4. The variation application form should clearly outline the "present" and "proposed" VAMF EMA Certificate (code number) in the MA dossier. When applicable, the variation application form should clearly list also all the other VAMFs to which the medicinal product refers even if they are not the subject of the application.			

B.V.b) Referral

B.V.b.1 Update of the quality dossier intended to implement the outcome of a Union referral procedure	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) The change implements the outcome of the referral	**1**	**1, 2**	**IA$_{IN}$**
b) The harmonisation of the quality dossier was not part of the referral and the update is intended to harmonise it			**II**
Conditions			
1. The outcome does not require further assessment.			
Documentation			
1. Attached to the cover letter of the variation application: A reference to the Commission Decision concerned.			
2. The changes introduced during the referral procedure should be clearly highlighted in the submission.			

C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES

C.I HUMAN MEDICINAL PRODUCTS

C.I.1 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) The medicinal product is covered by the defined scope of the procedure	**1**	**1, 2, 3**	**IA$_{IN}$**
b) The medicinal product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure and no new additional data is required to be submitted by the MAH		**1, 2, 3**	**IB**
c) The medicinal product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure with new additional data submitted by the MAH		**1, 3**	**II**
Conditions			
1. The variation implements the wording requested by the authority and it does not require the submission of additional information and/or further assessment.			
Documentation			
1. Attached to the cover letter of the variation application: a reference to the Commission Decision concerned or to the agreement reached by the CMDh (as applicable) with the annexed Summary of Product Characteristics, Labelling or Package Leaflet.			
2. A declaration that the proposed Summary of Product Characteristics, Labelling and Package Leaflet is identical for the concerned sections to that annexed to the Commission Decision or to the agreement reached by the CMDh (as applicable).			
3. Revised product information.			

C.I.2 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) Implementation of change(s) for which no new additional data is required to be submitted by the MAH		**1, 2**	**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**
Documentation			
1. Attached to the cover letter of the variation application: EMA/NCA request, if applicable.			
2. Revised product information.			

C.I.3 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of Regulation 1901/2006	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) Implementation of wording agreed by the competent authority	**1**	**1, 2**	**IA_{IN}**
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH		**2**	**II**
Conditions			
1. The variation implements the wording requested by the competent authority and it does not require the submission of additional information and/or further assessment.			
Documentation			
1. Attached to the cover letter of the variation application: reference to the agreement/assessment of the competent authority.			
2. Revised product information.			

C.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	Conditions to be fulfilled	Documentation to be supplied	Variation type
			II
Note: This variation does not apply when the new data has been submitted under variation C.I.13. In such cases, the change(s) in the SmPC, labelling and/or package leaflet is covered by the scope of variation C.I.13.			

C.I.5 Available for medicinal products authorised through the centralised procedure	Variation type

C.I.6 Change(s) to therapeutic indication(s)	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) Addition of a new therapeutic indication or modification of an approved one			**II**
b) Deletion of a therapeutic indication			**IB**
Note: Where the change takes place in the context of the implementation of the outcome of a referral procedure, or -for a generic/hybrid/biosimilar product- when the same change has been done for the reference product, variations C.I.1 and C.I.2 apply, respectively.			

C.I.7 Not available for medicinal products authorised by the NAMMD (see *Note*)	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) Pharmaceutical forms		**1, 2**	**IB**
b) Strengths		**1, 2**	**IB**
Note: In cases where a given pharmaceutical form or strength has received from the NAMMD a marketing authorization which is separate to the marketing authorization for other pharmaceutical forms or strengths, the deletion of the former will not be a variation but the withdrawal of the marketing authorization.			

C.I.8 Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use*	Conditions to be fulfilled	Documentation to be supplied	Variation type
a) Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details)		**1, 2**	**IA_{IN}**

and/or changes in the Pharmacovigilance System Master File (PSMF) location			

Documentation

1. Summary of the pharmacovigilance system, or update of the relevant elements (as applicable):

- Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance and an affidavit signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC;
- Contact details of the QPPV, Member States in which the QPPV resides and carries out his/her tasks;
- PSMF location.

2. PSMF (if available)

Note: This variation covers the introduction of a PSMF irrespective of whether or not the technical dossier of the MA contained a DDPS.

Once the database mentioned in Article 57 of Regulation (EU) no. 1235/2010 on amendment of Regulation (EC) no. 726/2004 is functional, changes in QPPV, including contact details (telephone and fax numbers, postal address and email address) and changes to the location of the PSMF (street, city, postcode, country) may be updated through the Article 57 database only (without the need for a variation).

Where the MAH makes use of the possibility to update the above information through the Article 57 database, the MAH must indicate in the marketing authorisation that the updated information of those particulars is included in the database.

C.I.9 Change(s) to an existing pharmacovigilance system as described in the detailed description of the pharmacovigilance system (DDPS).	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) Change in the QPPV and/or QPPV contact details and/or back-up procedure	**1**	**1**	**IA_{IN}**
b) Change(s) in the safety database and/or major contractual arrangements for the fulfilment of pharmacovigilance obligations, and/or change of the site undergoing pharmacovigilance activities	**1, 2, 3**	**1**	**IA_{IN}**
c) Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system (e.g. change of the major storage/archiving location, administrative changes)	**1**	**1**	**IA**
d) Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	**4**	**1, 2**	**IA_{IN}**

Conditions

1. The pharmacovigilance system itself remains unchanged.
2. The database system has been validated (when applicable).
3. Transfer of data from other database systems has been validated (when applicable).
4. The same changes to the DDPS are introduced for all medicinal products of the same MAH (same final DDPS version)

Documentation

1. Latest version of the DDPS and, where applicable, latest version of the product specific addendum. These should include for changes to the QPPV a) summary CV of the new QPPV, b) proof of QPPV EudraVigilance registration, and c) a new statement of the MAH and the QPPV regarding their availability and the means for notification of adverse reactions signed by the new QPPV and the MAH, and reflecting any other consequential changes, e.g. to the organisational chart.

   When the QPPV and /or QPPV contact details are not included in a DDPS or no DDPS exists, the submission of a revised DDPS version is not required and the application form is to be provided.
2. Reference of the application/procedure and product in which the change(s) were accepted.

Note: C.I.9 covers changes to an existing pharmacovigilance system for human medicinal products that have not yet introduced a PSMF.

Note for a): Once the Article 57 database is functional, changes in QPPV, including contact details (telephone and fax numbers, postal address and email address) may be updated through the Article 57 database only (without the need for a variation). Where the MAH makes use of the possibility to update this information through the Article 57 database, the MAH must indicate in the marketing authorisation that the updated information of those particulars is included in the database.

Note for d): The assessment of a DDPS submitted as part of a new MAA/Extension/Variation may give rise to changes at the request of the NAMMD in this DDPS. Where this occurs, the same change(s) can be introduced to the DDPS in other marketing authorisations of the same MAH by submitting a (grouped) Type IA_{IN} variation.

C.I.10 Change in the frequency and/or date of submission of periodic safety update reports (PSUR) for human medicinal products	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	**1, 2**	**IA_{IN}**
Conditions			
1. The change in the frequency and/or date of submission of the PSUR has been agreed by the CHMP/CMDh/NAMMD			
Documents			
1. Attached to the cover letter of the variation application: A reference to the agreement of the NAMMD			
2. Revised frequency and/or date of submission of the PSUR.			
Note: This variation applies only when the PSUR cycle is specified in the marketing authorisation by other means than a reference to the EU list of reference data and where PSUR submission is required.			

C.I.11 Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) **Implementation of wording agreed by the NAMMD**	**1**	**1, 2**	**IA_{IN}**
b) **Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the NAMMD is required***			**II**
Conditions			
1. The variation implements the action requested by the authority and it does not require the submission of additional information and/or further assessment.			
Documentation			
1. Attached to the cover letter of the variation application: A reference to the relevant decision of the NAMMD.			
2. Update of the relevant section of the dossier.			
Note: This variation covers the situation where the only change introduced concerns the conditions and/or obligations of the marketing authorisation, including the risk management plan and the conditions and/or obligations of marketing authorisations under exceptional circumstances and conditional marketing authorisation. *The introduction of a risk management plan requested by the NAMMD always requires significant assessment.			

C.I.12 Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	**1, 2**	**IA_{IN}**
Conditions			
1. The medicinal product is included or removed from the list of medicinal products that are subject to additional monitoring (as applicable)			
Documentation			

1. Attached to the cover letter of the variation application: A reference to the list of medicinal products that are subject to additional monitoring
2. Revised product information
Note: This variation covers the situation where the inclusion or deletion of the black symbol and explanatory statements is not done as part of another regulatory procedure (e.g. renewal or variation procedure affecting the product information).

C.I.13 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the NAMMD*	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
			II
Note: In cases where the assessment by the competent authority of the data submitted leads to a change of the Summary of Product Characteristics, Labelling or Package Leaflet, the relevant amendment to the Summary of Product Characteristics, Labelling or Package Leaflet is covered by the variation. The inclusion of the Compliance Statement provided for under Article 28(3) of Regulation 1901/2006 is likewise covered by this variation (provided that the requirements under Regulation 1901/2006 have been met). * This variation does not apply to variations that can be considered as Type IB by default under any other section of this Annex.			

C.II Not available for medicinal products for human use	**Variation type**

D. PMF/VAMF

D.1 **Change in the name and/or address of the VAMF certificate holder**	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	**1**	**IA_{IN}**
Conditions			
1. The VAMF certificate holder must remain the same legal entity.			
Documentation			
1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.			

D.2 Change in the name and/or address of the PMF certificate holder	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	**1**	**IA_{IN}**
Conditions			
1. The PMF certificate holder must remain the same legal entity.			
Documentation			
1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.			

D.3 Change or transfer of the current PMF certificate holder to a new PMF certificate holder -i.e. different legal entity).	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
		1, 2, 3, 4, 5, 6	**IA_{IN}**
Documentation			
1. A document including the identification (name and address) of the current PMF Holder (transferor) and the identification (name and address) of the person to whom the transfer is to be granted (transferee) together with the proposed implementation date – signed by both companies.			
2. Copy of the latest PMF Certificate page 'EMA Plasma Master File (PMF) Certificate of compliance with Community legislation'.			
3. Proof of establishment of the new holder (Excerpt of the commercial register and the English translation of it) - signed by both companies.			

4.	Confirmation of the transfer of the complete PMF documentation since the initial PMF certification to the transferee - signed by both companies.
5.	Letter of Authorisation including contact details of the person responsible for communication between the competent authority and the PMF holder - signed by the transferee.
6.	Letter of Undertaking to fulfil all open and remaining commitments (if any) - signed by the transferee.

D.4 Change in the name and/or address of a blood establishment including blood/plasma collection centres	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1, 2	**1, 2, 3**	**IA**
Conditions			
1. The blood establishment must remain the same legal entity.			
2. The change must be administrative (e.g. merger, take over); change in the name of the blood establishment/ collection centre provided the blood establishment must remain the same.			
Documentation			
1. Signed declaration that the change does not involve a change of the quality system within the blood establishment.			
2. Signed declaration that there is no change in the list of the collection centres.			
3. Updated relevant sections and annexes of the PMF dossier.			

D.5 Replacement or addition of a blood/plasma collection centre within a blood establishment already included in the PMF	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
		1, 2, 3	**IB**
Documentation			
1. Epidemiological data for viral markers related to the blood/plasma collection centre covering the last 3 years. For newly opened centre(s) or in case no data are yet available, a declaration that epidemiological data will be provided at the time of the next annual update(s).			
2. Statement that the centre is working under the same conditions as the other centres belonging to the blood establishment, as specified in the standard contract between blood establishment and PMF holder.			
3. Updated relevant sections and annexes of the PMF dossier.			

D.6 Deletion or change of status (operational/non-operational) of establishment(s)/centre(s) used for blood/plasma collection or in the testing of donations and plasma pools	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1, 2	**1**	**IA**
Conditions			
1. The reason for deletion or change of status should not be related to a GMP issue.			
2. The establishments(s)/centre(s) should comply with the legislation in terms of inspections in case of change of status from non-operational to operational.			
Documentation			
1. Updated relevant sections and annexes of the PMF dossier.			

D.7 Addition of a new blood establishment for the collection of blood/plasma not included in the PMF	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
			II

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	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**

		1, 2	**IB**
Documentation			
1. Statement that the testing is performed following the same SOPs and/or test methods as already accepted.			
2. Updated relevant sections and annexes of the PMF dossier.			

D.9 Addition of a new blood establishment for testing of donations and/or plasma pool not included in the PMF	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
			II

D.10 Replacement or addition of a new blood establishment or centre(s) in which storage of plasma is carried out	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
		1, 2	**IB**
Documentation			
1. Statement that the storage centre is working following the same SOPs as the already accepted establishment.			
2. Updated relevant sections and annexes of the PMF dossier.			

D.11 Deletion of a blood establishment or centre(s) in which storage of plasma is carried out	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	**1**	**IA**
Conditions			
1. The reason for deletion should not be related to a GMP issues.			
Documentation			
1. Updated relevant sections and annexes of the PMF dossier.			

D.12 Replacement or addition of an organisation involved in the transport of plasma.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
		1	**IB**
Documentation			
1. Updated relevant sections and annexes of the PMF dossier, including a list of all the blood establishments using this transport organisation, a summary of the system in place to ensure that the transport is performed under appropriate conditions (time, temperature and GMP compliance) and confirmation that transport conditions are validated.			

D.13 Deletion of an organisation involved in the transport of plasma	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	**1**	**IA**
Conditions			
1. The reason for deletion should not be related to GMP issues.			
Documentation			
1. Updated relevant sections and annexes of the PMF dossier.			

D.14 Addition of a CE-marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	**1, 2**	**IA**
Conditions			
1. The new test kit is CE-marked.			
Documentation			
1. List of testing site(s) where the kit is used.			

2.	Updated relevant sections and annexes of the PMF dossier, including updated information on testing as requested in the "Guideline on the scientific data requirements for a PMF".

D.15 Addition of a non-CE marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit	**Conditions to be fulfilled**	**Documentation to be supplied**	**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		**1, 2**	**IA**
Documentation			
1. List of testing centre(s) where the kit is currently used and a list of testing centre(s) where the kit will be used.			
2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing as requested in the "Guideline on the scientific data requirements for a PMF".			

D.16 Change of kit/method used to test pools (antibody or antigen or NAT test).	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
			II

D.17 Introduction or extension of inventory hold procedure.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
	1	**1**	**IA**
Conditions			
1. The inventory hold procedure is a more stringent procedure (e.g. release only after retesting of donors).			
Documentation			
1. Updated relevant sections of the PMF dossier, including the rationale for introduction or extension of inventory hold period, the sites where the inventory hold takes place and for changes to procedure, a decision tree including new conditions.			

D.18 Removal of inventory hold period or reduction in its length.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
		1	**IB**
Documentation			
1. Updated relevant sections of the PMF dossier			

D.19 Replacement or addition of blood containers (e.g. bags, bottles)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) The new blood containers are CE-marked	**1, 2**	**1**	**IA**
b) The new blood containers are not CE-marked			**II**
Conditions			
1. The container is CE-marked.			
2. The quality criteria of the blood in the container remain unchanged.			
Documentation			
1. Updated relevant sections and annexes of the PMF dossier, including the name of container, manufacturer, anticoagulant solution specification, confirmation of CE-mark and the name of the blood establishments where the container is used.			

D.20 Change in storage / transport	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
a) storage and/or transport conditions	**1**	**1**	**IA**

b) maximum storage time for the plasma	**1, 2**	**1**	**IA**
Conditions			
1. The change should tighten the conditions and be in compliance with Ph. Eur. requirements for Human Plasma for Fractionation.			
2. The maximum storage time is shorter than previously.			
Documentation			
1. Updated relevant sections and annexes of the PMF dossier, including detailed description of the new conditions, confirmation of validation of storage/transport conditions and the name of the blood establishment(s) where the change takes place (if relevant).			

D.21 Introduction of test for viral markers when this introduction will have significant impact on the viral risk assessment.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
			II

D.22 Change in the plasma pool preparation (e.g. manufacturing method, pool size, storage of plasma pool samples)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
		1	**IB**
Documentation			
1. Updated relevant sections of the PMF dossier.			

D.23 Change in the steps that would be taken if it is found retrospectively that donation(s) should have been excluded from processing ("look-back" procedure).	**Conditions to be fulfilled**	**Documentation to be supplied**	**Variation type**
			II

ANNEX 2
to SCD no. 19/12.08.2013

APPLICATION FORM FOR
VARIATION TO A MARKETING AUTHORISATION

HUMAN ☐ **VETERINARY** ☐

Variation procedure number(s)[3]:.....

☐ **NATIONAL AUTHORISATION IN MRP**
☐ **CENTRALISED 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 ☐NICIUNUL

Type of application (tick all applicable options)

☐ **Type IA$_{IN}$**
☐ **Type IA**
☐ **Type IB unforeseen[4]**
☐ **Type IB**
☐ **Type II**
☐ **Type II Art. 29[5]**

☐ **Single variation**
☐ **Grouping of variations**
☐ **Including a line extension[6]**
☐ **Worksharing**

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[3] 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' EMEA 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 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 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.

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

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

Name and address of the Applicant/MA holder[7]:	Name and address of contact person[8]: Telephone number: Fax number (optional): E-mail:

MEDICINAL PRODUCTS CONCERNED BY THIS APPLICATION[9]

Invented name(s) of the medicinal product(s):	Active substance(s)	Pharmaceutical form	Strength	MA Holder name(s)	MA number(s)[10]	MRP variation number

[4] Type II variation submitted under Article 29 of Regulation (EC) No 1901/2006.
[5] For worksharing or grouped variations affecting more than one Marketing Autorisation (MA), indicate the MAH to be used as reference MAH for the handling of the procedure.
[6] In accordance with the provisions of section 2.4.3 of 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).
[9] If the List is very long (longer than one page), it could be attached as an annex to the variation application.
For centrally authorised medicinal products, Annex A of the medicinal product(s) subject to the application should be attached as and annex to the variation application.
For the worksharing procedure submitted to the EMA, including nationally authorised medicinal products, the details referring to the medicinal products and to the concerned Member States should be attached as Annex B to the variation application (please check the mock-up on the EMA website).
[10] Se indică numerele APP-urilor care fac obiectul cererii (un interval, dacă este adecvat). For variation number, specific to the medicinal product, see the *Best Practice Guide for the handling of variations*, Chapter 1, e.g. NL/H/0123/001-004/IB/033/G

TYPE 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		Variation 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 [10],[11]	**PROPOSED**
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]

[11] If needed, the D-U-N-S number shall be included. The Data Universal Numbering System (D-U-N-S)] is a system developed by Dun & Bradstreet (D&B), assigning an unique digital identifier to a single commercial entity. In this case, it is used to facilitate the manufacturing sites outside the EEA.

[12] If needed, the EU or national ASMF number shall be included (only if the reference EU ASMF is unavailable)

[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 THERAPEUTIC 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 EU Register of Orphan Medicinal Products:
☐ Attach copy of the Designation decision

❍ Orphan designation refused
Date (yyyy-mm-dd):
Reference number of the European Commission Decision:

❍ 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 medicinal 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: Please repeat, if required

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 700 (3) of Law 95/2006, as amended, transposing Article 6 (1), the second 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 (EEC) 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:

❍ **THIS APPLICATION DOES NOT FALL WITHIN THE SCOPE OF ARTICLE 8 OF THE PAEDIATRIC REGULATION, SINCE:**
- ❍ The medicinal product is not protected by a supplementary certificate under Regulation (EC) no. 469/2009 or by a patent which qualifies for granting of the supplementary protection certificate
- ❍ This application relates to a marketing authorisation for a medicinal product with a well-established medical use, generic, a hybrid, biosimilar or herbal medicinal product

❍ **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 THE 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/Waiver decision is to be included in Module 1.10, as well as a copy of the opinion of the Paediatric Committee (PDCO))
HAS THIS APPLICATION BEEN SUBJECT TO PIP COMPLIANCE VERIFICATION?
❍ No
❍ Yes
If YES, please specify the reference compliance report:
(Note: If available, a copy of the PDCO opinion + report, document issued by the national competent authority is to be included in Module 1.10)
☐ The summary of PIP outcomes in a tabulated form is included in module 1.10

Type II variations – Extended data/market exclusivity:
(Delete this section if not applicable)

THIS REQUEST IS ALSO SUPPORTED BY THE FOLLOWING ARTICLES OF LAW 95/2006 ON HEALTHCARE REFORM, AS AMENDED (HEREINAFTER THE LAW) OR BY REGULATION (EC) 726/2004:

[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] Check if PIP opinion refers to a waiver
[16] Check only if this is about a product-specific waiver opinion, covering all subgroups of the paediatric population

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

❍ Article 704 (1) of the Law/Article 14 (11) of Regulation (EC) no. 726/2004 (one year of data exclusivity for a new indication)
❍ Article 704 (5) of the Law (one year of data exclusivity for a new indication)
❍ Article 785 of the Law (one year of data exclusivity for a change in classification)

(Note: The report justifying the claim for extended data/market exclusivity 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

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;
- ☐ The evaluation fee has 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 both the RMS/CMS (as required) 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: _____

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[17] Only for centrally authorised products (Annex II of EU MA).

[18] See Chapter 7 of Volume 6A of the *Notice to Applicants* or of the *Transfer of Information* from the *Notice to Applicants*, Volume 2A, Chapter 7 (http://www.hma.eu) or *Requirements concerning the dossier of centrally authorised medicinal products* (http://www.ema.europa.eu).

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

Fees paid *Amount*[20] _____

Please specify fee category in accordance with national regulations _____

Main signatory[21]_____ Status (job title)
_____

Print name _____

Date _____

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

Second signatory _____

Print name_____ Status (job title)
_____

Date _____

[20] For submissions to the EMA (including worksharing procedures which include MRP products and/or purely national medicinal 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(s) 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		**Variation 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		**Variation 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		**Variation 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 changes		Variation type	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

		Variation 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		Variation 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.

		Variation type		
☐ **A.3**	**Change in the name of an 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.

		Variation type		
☐ **A.4**	**Change in the name and/or address of a manufacturer (including where relevant quality control sites) or holder of the Active Substance Master File (ASMF), supplier of the active substance, starting material (where specified in the product dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or of the manufacturer of a new excipient (where specified in the product 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 quality/testing control sites]		Variation type		
☐ a)	Batch release is one of the attributions of the manufacturer/importer	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ b)	Batch release is not the attribution of the manufacturer/importer	☐IA	☐IB¤	**Implement. date:**

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

		Variation 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.

		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¤	**Implement. date:**

¤ If one of the conditions is not met and the change is not specifically listed as Type II.
*Note: If the authorities have announced their intention to perform an inspection, the deletion of a concerned site should be announced immediately.

		Variation type	
☐ **A.8**	**Change in the date of performance of the audit related to checking compliance with Good Manufacturing Practices (GMP) by the manufacturer of an active substance***	☐IA	**Implement. date:**

B.I.a Change in the manufacture of the active substance	Variation 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 sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	Variation 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 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 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) Addition of a new manufacturer of the active substance without ASMF requiring a significant update of the dossier section referring to the respective active substance	II		
☐ h) Addition of an alternative sterilisation site for the active substance, using a method of the European Pharmacopoeia	IB		
☐ i) Introduction of a new micronisation site	☐IA	☐IB¤	
☐ j) Changes to the testing process for quality control of a biological active substance: replacement or addition of a site of batch control/testing, including a biological/immunological/immunochemical method	II		
☐ k) New site for storage of the 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		**Variation 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 medicinal product, which may have a significant impact upon the product's quality/safety and efficacy, 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/closed 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 manufacture of the active substance		**Variation type**		
☐ a)	Up to 10-fold increase compared to the currently 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 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 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		Variation type		
☐ a)	Tightening of in-process limits	☐IA	☐IB¤	**Implement. date:**
☐ b)	Addition of new in-process tests 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		Variation type
☐ a)	Replacement of the strain(s) in a seasonal, pre-pandemic or a pandemic vaccine against human influenza	II

B.I.b Changes in the control of the active substance		Variation 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		Variation type		
☐ a)	Tightening of specification limits for medicinal products subject to Official Batch Release	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ b)	Tightening of specification limits	☐IA	☐IB¤	**Implement. date:**
☐ c)	Addition of a new testing parameter 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 active substances) of a specification parameter 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		**Variation 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)	Change or replacement to 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		**Variation type**	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5** **Implement. date:**

B.I.c.1 Change in immediate packaging of the active substance		**Variation type**		
☐ a)	Qualitative and/or quantitative composition	☐IA	☐IB¤	**Implement. date:**
☐ b)	Qualitative and/or quantitative composition for sterile and nonfrozen 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		**Variation 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		**Variation 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.			**Variation 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 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 in 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:		**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_{IN}	☐IB¤	**Implement. date:**

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

B.I.e.4 Change in description and composition of the Finished Product		**Variation type**	
☐ a)	Major changes in the approved protocol concerning the handling of changes	II	
☐ b)	Minor changes in the approved protocol concerning the handling of changes, not affecting the strategy defined in the protocol	IB	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

B.I.e.5 Implementation of the changes mentioned in an approved protocol related to the management of changes		**Variation type**	
☐ a)	The implementation of the change does not require additional justifying data	☐IA_{IN}	☐IB¤
☐ b)	The implementation of the change requires additional justifying data	IB	

☐	c)	The implementation of a change concerning 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 Changes in the description and composition of the medicinal product			**Variation 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.			**Variation 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			**Variation 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 anew kit for a pharmaceutical preparation with another filling 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			**Variation 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			**Variation 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.

	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 primary packaging**	IB

B.II.b Change in manufacture of the Finished Product			**Variation 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		**Variation 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 obtained through 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 sterile medicinal products manufactured using an aseptic method 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 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¤	**Implement. date:**
☐ b)	Replacement or addition of a manufacturer responsible for batch release for a biological/immunological medicinal product, any of the test methods performed at the respective site being a biological/immunological method	II		
c)	Replacement or addition of a manufacturer responsible for batch import and/or 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 one 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 and of an intermediate used in the manufacture of the finished product		**Variation 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 medicinal 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 overdosage 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		**Variation 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	**Variation type**

☐ a)	Tightening of in-process limits	☐IA	☐IB¤	**Implement. date:**
☐ b)	Addition of new tests 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 the overall quality of the finished product	II		
☐ f)	Addition or replacement of an in-process test as a result of a safety 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		**Variation 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		**Variation type**		
☐ a)	Tightening of specification limits	☐IA	☐IB¤	**Implement. date:**
☐ b)	Addition of a new specification parameter (e.g. deletion of an obsolete parameter)	☐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 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.II.c.2 Change in test procedure for an excipient			Variation 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 biochemical 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			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¤	**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 of a new excipient			Variation type		
☐	a)	Minor change in synthesis or recovery of a nonpharmacopoeial excipient or of a new 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			Variation 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		Variation type		
☐ a)	Tightening of specification limits	☐IA	☐IB¤	**Implement. date:**
☐ b)	Tightening of specification limits for medicinal products subject to Official Batch Release	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ c)	Addition of a new specification parameter (e.g. deletion of an obsolete parameter)	☐IA	☐IB¤	**Implement. date:**
☐ d)	Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter, e.g. smell and taste, or of the identification test for a colouring/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 products) of a specification parameter and of the corresponding test method as a result of a safety or quality issue	IB		
☐ h)	Update of the dossier in accordance with the provisions of an updated general monograph of the European Pharmacopoeia for the medicinal product*	☐IA_{IN}	☐IB¤	
☐ i)	Introduction of the provisions of the European Pharmacopoeia 2.9.40 (Uniformity of dosage units) for replacement of the currently approved method, either European Pharmacopoeia 2.9.5 (Uniformity of mass) or European Pharmacopoeia 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		Variation 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 biochemical reagent or replacement of a biological reference preparation which is not part of an approved protocol	II		
☐ d)	Other changes to a test procedure (including replacement or addition)	IB		
☐ e)	Update of the test procedure in accordance with the updated general monograph of the European Pharmacopoeia	☐IA	☐IB¤	

☐ f)	To reflect compliance with the European Pharmacopoeia And to eliminate the obsolete reference to the internal testing method and to the testing method code*	☐IA	☐IB¤

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

	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 Change in container closure system of the Finished Product			**Variation type**	
☐ z)	Other variation		☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

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¤	**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 the type of recipient or addition of a new one				
☐	1.	Solid, semi-solid and non-sterile liquid pharmaceutical forms	IB		
☐	2.	Sterile medicinal products and biological/ immunological medicinal products	II		
☐	3.	Deletion of a container meant for immediate packaging, which does not lead to the entire deletion of a strength/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			**Variation 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		**Variation 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)		**Variation 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		**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¤	**Implement. date:**
☐	2. Change outside the range of the currently approved pack sizes	IB		
☐ b)	Deletion of a 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, and biological/ immunological multidose parenteral medicinal products.	II		
☐ d)	Change in the fill weight/fill volume of non-parenteral multidose (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))		**Variation 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)		**Variation 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			**Variation 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 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		
☐ e)	Change in 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, 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

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

		Variation type		
☐	**B.II.g.3 Deletion of an approved change management protocol related to the finish 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.II.g.4 Changes on the approved protocol concerning the handling of changes		**Variation type**	
☐ a)	Major changes in the approved protocol concerning the handling of changes	II	
☐ b)	Minor changes in the approved protocol concerning the handling of changes, not affecting the strategy defined in the protocol	IB	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

B.II.g.5 Implementation of the changes mentioned in an approved protocol for handling of changes		**Variation type**		
☐ a)	The implementation of the change does not require additional supporting data	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ b)	The implementation of the change requires additional supporting data	IB		
☐ c)	The implementation of a change concerning 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 of the information in „ Adventitious Agents Safety Evaluation" (Section 3.2.A.2)		**Variation 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**			**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¤	**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		**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¤	**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		**Variation type**	
☐ z)	Other variations	☐IA ☐IB ☐ II	☐ **Art 5 Implement. date:**

B.IV.1 Change of a measuring or administration medical 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	☐ IAIN	☐ IB¤	**Implement. date:**
☐ 2.	Device without CE marking (for veterinary products only)	IB		
☐ 3.	Spacer device for metered dose inhalers or another device which may have a major impact on the release of the product's active substance (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	**Variation type**

☐ a)	Tightening of specification limits	☐IA	☐IB¤	**Implement. date:**
☐ b)	Addition of a new specification parameter (e.g. deletion of an obsolete parameter)	☐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		**Variation 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.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¤	**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)		**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¤	**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 in view of enforcement of the outcome of a referral procedure at EU level		**Variation 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		**Variation 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 in view of implementation of the outcome of the referral procedure at EU level		**Variation type**		
☐ a)	The medicinal product is covered by the defined scope of the referral*	☐IA_{IN}	☐IB¤	**Implement. date:**
☐ 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		

¤ 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		**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 Change(s) in the Summary of Product Characteristics, labelling or leaflet of medicinal products for human	**Variation type**

	use in view of implementation of the outcome of a procedure related to Periodic Safety Update Reports (PSURs) or of Post Authorisation Safety Studies (PASSs) or of the outcome of the assessment performed by a competent authority in accordance with Article 45/46 of Regulation (EC) No 1901/2006			
☐ a)	Implementation of the wording change 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.

C.I.4 Change(s) in the Summary of Product Characteristics, labelling or package leaflet due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	**Variation type**
☐	II

C.I.5 Change in the legal status of a medicinal product for centrally authorised products		**Variation 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)		**Variation 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:		**Variation type**
☐ a)	A pharmaceutical form	IB
☐ b)	A strength	IB

C.I.8 Introduction of a new summary of the Pharmacovigilance system for medicinal products for human use or of its change*		**Variation 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 DDPS.		**Variation type**		
☐ a)	Change in QPPV and/or his/her contact details and/or of the back-up procedure of the QPPV	☐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.

	Variation 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		**Variation type**		
☐	a)	Implementation of wording agreed by the NAMMD	☐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 NAMMD 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.

	Variation 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.

	Variation type
C.I.13 Other variations which are not specifically included in another section of this Annex and which require the submission of trials to the NAMMD* ☐	II

C.II Changes to veterinary medicinal products		**Variation type**	
☐	z) Other variation	☐IA ☐IB ☐II	☐ **Art 5** **Implement. date:**

	Variation 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.	**Variation type**
☐ a) Deletion as a result of a safety issue	II
☐ b) Deletion not resulting from a safety issue	IB

	Variation type
C.II.3 ☐ **Changes to the withdrawal period for a veterinary medicinal product**	II

	Variation 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

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

		Variation 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 variation	IB

C.II.7 Introduction of a new pharmacovigilance system		**Variation type**
☐ a)	Which has been assessed by the relevant national competent authority/EMA for another medicinal product of the same Marketing Authorisation Holder	II
☐ b)	Which has not been assessed by the relevant national competent authority/EMA for another medicinal product of the same Marketing Authorisation Holder	IB

	Variation 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		**Variation type**	
☐ z)	Other variation	☐IA ☐IB ☐II	☐ **Art 5 Implement. date:**

	Variation 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.

		Variation 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.

		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¤	**Implement. date:**

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

		Variation 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.

		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¤	**Implement. date:**

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

		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 pools 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¤	**Implement. date:**

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

	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¤	**Implement. date:**

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

		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¤	**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**	**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¤	**Implement. date:**

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

		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¤	**Implement. date:**

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

		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¤	**Implement. date:**
☐ b)	The new blood containers are not EC-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**	**Variation 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.

		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