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Guidelines 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 on the documentation to be submitted pursuant to those procedures

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1. INTRODUCTION

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 as amended [1] ('the Variations Regulation') governs the procedure for the variation of marketing authorisations. .

Article 4(1) of the Variations Regulation charges the Commission with the task of drawing and updating up guidelines 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 that Regulation as well as on the documentation to be submitted pursuant to these procedures.

These guidelines apply to the variations of marketing authorisations for medicinal products for human use granted in accordance with Regulation (EC) No 726/2004 of the European Parliament and of the Council [3], Directive 2001/83/EC [5] of the European Parliament and of the Council. They are intended to facilitate the interpretation and application of the Variations Regulation. They provide details on the application of the relevant procedures, including a description of the relevant steps from the submission of an application for a variation to the final outcome of the procedure on the application.

In addition, the Annex to these guidelines 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 and provides further details, where appropriate, on the scientific data to be submitted for specific variations and how this data should be documented.

These guidelines will be regularly updated, taking into account the recommendations provided in accordance with Articles 4 and 5 of the Variations Regulation. The electronic version of these guidelines, including any new classifications of variations and the updates published by the Commission on its website, as well as any recommendation issued in accordance with Article 5 of the Variations Regulation and not yet integrated should be followed.

Definitions relevant to these guidelines are provided in Directive 2001/83/EC as well as in the Variations Regulation. In addition, for the purpose of these guidelines, marketing authorisation holders belonging to the same mother company or group of companies and marketing authorisation holders having concluded agreements or exercising concerted practices concerning the placing on the market of the relevant medicinal product have to be taken as the same marketing authorisation holder [7] ('holder').

Reference in these guidelines to the 'centralised procedure' is to be understood as the procedure for granting marketing authorisations set out in Regulation (EC) No 726/2004. Reference to the 'mutual recognition procedure' and 'decentralised procedure' is to be understood as the procedure for granting marketing authorisations as set out in chapter 4 of Directive 2001/83/EC. Reference to the 'purely national procedure' is to be understood as the procedure for granting marketing authorisations by a Member State in accordance with the *acquis* outside the mutual recognition and decentralised procedure.

Reference in these guidelines to 'variations for mutual recognition procedure' is to be understood as the variation procedures conducted for applications concerning marketing authorisations granted in accordance with Chapter 4 of Directive 2001/83/EC as described above (both via the 'mutual recognition procedure' and the 'decentralised procedure').

Reference to ‘concerned Member States’ is to be understood as all Member States concerned except the reference Member State. Reference to ‘national competent authority’ is to be understood as the authority that has granted a marketing authorisation under a purely national procedure.

Reference in these guidelines to the Agency means the European Medicines Agency.

2. PROCEDURAL GUIDANCE ON THE HANDLING OF VARIATIONS

A marketing authorisation lays down the terms under which the marketing of a medicinal product is authorised in the EU. A marketing authorisation is composed of:

(i) a decision granting the marketing authorisation issued by the relevant authority; and
(ii) a technical dossier with the data submitted by the holder in accordance with Article 8(3) to Article 11 of Directive 2001/83/EC and Annex I thereto, Articles 6(2) of Regulation (EC) No 726/2004, or Article 7 of Regulation (EC) No 1394/2007.

The Variations Regulation governs the procedures for the amendment of the decision granting the marketing authorisation and of the technical dossier.

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. In accordance with Article 61(3) of Directive 2001/83/EC, these changes are to be notified to the relevant competent authorities and they may be implemented if the competent authority has not objected within 90 days.

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 restrictions

Submission requirements for a variation application:

An application for variation shall be made electronically in the formats made available by the relevant authority and 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 rules governing medicinal products in the European Union’, Volume 2B, Notice to applicants (‘EU-CTD’) format):

- Cover letter.
- The completed electronic EU variation application form (eAF) (published under https://esubmission.ema.europa.eu/eaf/index.html), including the details of the marketing authorisation(s) concerned, as well as a description of all individual variations submitted, together with their date of implementation and an indication that all conditions and documentation requirements are met for type IA and IB variations, as applicable. A detailed present and proposed table for all changes included in the submission should also be provided. 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 eAF. Where a variation is considered unclassified, a detailed justification for its submission as a Type IB notification must be included.

- Relevant documentation/data in support of the proposed variation(s) including any documentation specified in the Annex to these guidelines, where applicable.
- In case that the variation(s) affect the summary of product characteristics, labelling, package leaflet, or the obligations and conditions of a centrally authorised marketing authorisation: the revised product information presented in the appropriate format. For minor variations of type IA or IB the relevant translations should also be provided at submission, whereas in the remaining cases they should be provided at the latest immediately after a positive opinion on the procedure for centrally authorised medicinal products or, respectively, within 7 days after the end of procedure for mutual recognition procedure and decentralised procedure . Where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the variation, mock-ups or specimens should be provided to the reference Member State, the national competent authority, or the Agency, if applicable.
- For grouped variations concerning several marketing authorisations , a common cover letter and eAF should be submitted together with separate supportive documentation for each variation applied for and revised product information (if applicable) for each medicinal product concerned. This will allow the relevant authorities to update the dossier of each marketing authorisation included in the group with the relevant amended or new information.
- For variations requested by the 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.
- With the exception of minor variations of Type IA, and non-complex variations of Type IB (complex Type IB variations to be defined and published on the EMA and/or CMDh websites), an update or addendum 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.
- In case of extension(s) to the marketing authorisation supporting data relating to the proposed extension. Guidance on the appropriate additional studies required for extension applications is available in Appendix IV to Chapter 1 of Volume 2A of the Notice to applicants. Additionally, 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.

Further details on technical requirements regarding the submission of variations applications are available on the EMA and CMDh websites.

Any information related to the implementation of a given variation should be immediately provided by the holder upon the request of the relevant authority.

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.

Where justified, EMA and CMDh, as appropriate, may publish certain cases where related changes would be acceptable within a single variation application without grouping.

2.1. Minor variations of Type IA

Hereby guidance is provided on the application of Articles 7, 7a, 8, 11, 13a, 13d, 13e, 14, 17, 23 and 24 of the Variations Regulation to minor variations of Type IA.

The Variations Regulation and the Annex to these guidelines set out a list of changes to be considered as minor variations of Type IA.

The Annex to these guidelines clarifies the conditions which must be met in order for a change to follow a Type IA notification procedure and specifies which minor variations of Type IA must be notified immediately following implementation.

2.1.1. Submission of Type IA notifications

Minor variations of Type IA do not require prior examination by the authorities before they can be implemented by the holder. However, at the latest within 12 months from the date of the implementation, a notification of the variation must be submitted simultaneously to all concerned Member States, to the national competent authority, or to the Agency (as appropriate).

Type IA variations requiring immediate notification in accordance with the Annex to this guideline, should, in contrast to the above, be submitted immediately after implementation, in order to ensure continuous supervision of the medicinal product.

The holder may submit several minor variations of Type IA for the same marketing authorisation under a single notification, as established in Articles 7(2) and 13d(2) of the Variations Regulation("grouping"). For purely national procedures, such a notification can cover identical minor variations of Type IA for more than one marketing authorisation in the same Member State.

Super-grouping

In addition to the above, as established in Article 7a of the Variation Regulation, a group of variations of Type IA can be submitted in a single notification also for several marketing authorisations owned by the same holder, provided that the variations notified are identical for all marketing authorisations concerned ("super-grouping"). Super-grouping is possible in the following cases:

- One or several Type IA variations listed in chapters A and B of the Annex to this guideline are notified at the same time for several marketing authorisations approved via the mutual recognition procedure and/or decentralised procedure and/or purely national procedure in several Member States.
- One or several Type IA variations are notified at the same time for several marketing authorisations approved via the mutual recognition procedure and/or decentralised procedure and the reference Member State is the same.
- One or several Type IA variations are notified at the same time for several marketing authorisations approved via the centralised procedure.
- One or several Type IA variations are notified at the same time for several marketing authorisations approved via the mutual recognition procedure and/or decentralised procedure and/or purely national procedure in several Member States and the reference authority in consultation with the concerned authorities agree to the proposed super-grouping.

Annual reporting of type IA variations not requiring immediate notification

Notifications for a minor variations of type IA not requiring immediate notification shall be collected and submitted as an annual update or be submitted as part of a grouping together with variations of other types (as described in section 2.2.1 and 2.3.1 of this guideline), or be submitted as part of a super-grouping (as described above). The annual report must fulfil the conditions for grouping or super-grouping as specified above, if it concerns more than one Type IA variation.

Without acceptance from the relevant authorities, grouping of Type IA variations (not requiring immediate notification) for one marketing authorisation only (regardless of authorisation procedure) can only be used within the context of the annual update.

Individual notification of minor variations of type IA is only acceptable in the exceptional cases listed on the EMA and CMDh websites, or in justified cases when agreed with the national competent authority.

2.1.2. Type IA variations review for mutual recognition and purely national procedures

The reference Member State or national competent authority, as applicable, will review the Type IA notification within 30 days following receipt.

By Day 30, the reference Member State or national competent authority, as applicable, will inform the holder and if applicable the concerned Member States of the outcome of its review. In case the marketing authorisation requires any amendment to the decision granting the marketing authorisation, all Member States concerned will update the decision granting the marketing authorisation within 6 months following the receipt of the outcome of the review , provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the Member States concerned.

Where one or several minor variations of Type IA are submitted as part of one notification, the holder will be informed which variation(s) have been accepted or rejected following its review. The marketing authorisation holder must cease to apply/not implement the rejected variation(s), as applicable.

2.1.3. Type IA variations review for centralised procedure

The Agency will review the Type IA notification within 30 days following receipt, and a copy of the Type IA notification will be made available by the Agency to the rapporteur for information only.

By Day 30, the Agency will inform the holder of the outcome of its review. Where the outcome of the assessment is favourable and the Commission decision granting the marketing authorisation requires any amendment, the Agency will inform the Commission and transmit the revised documentation. In such case, the Commission will update the decision granting the marketing authorisation at the latest within 12 months.

Where one or several minor variations of Type IA are submitted as part of one notification, the Agency will clearly inform the holder which variation(s) have been accepted or rejected following its review. The marketing authorisation holder must cease to apply/not implement the rejected variation(s), as applicable.

2.2. Minor variations of Type IB

Hereby guidance is provided on the application of Articles 7, 9, 11, 13b, 13d, 13e, 15, 17, 23 and 24 of the Variations Regulation to minor variations of Type IB.

The Variations Regulation and the Annex to these guidelines set out a list of changes to be considered as minor variations of Type IB. Such minor variations must be notified before implementation. The holder must wait a period of 30 days to ensure that the notification is deemed acceptable by the relevant authorities before implementing the change ('Tell, Wait and Do' procedure).

2.2.1. Submission of Type IB notifications

Notifications for minor variations of Type IB must be submitted by the holder simultaneously to all Member States concerned, to the national competent authority or to the Agency (as appropriate).

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 reference Member State, the national competent, authority or the Agency (as appropriate).

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 in a single Member State, or one or more minor variation(s) of Type IB with other minor variations affecting several marketing authorisations in a single Member State provided that (i) the variations are the same for all the marketing authorisations concerned, (ii) the variations are submitted at the same time to the national competent authority, and (iii) the national competent authority has previously agreed to the grouping.

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 must submit these variations as one application for 'worksharing' (see section 3 on 'worksharing'). If a submission has been made as one or several variations but not including all affected marketing authorisations owned by the same holder in one application for 'worksharing', the holder will be informed and requested to revise its application.

2.2.2. Type IB variations review for mutual recognition and purely national procedures

Upon receipt of a Type IB notification, the notification will be handled as follows:

The reference Member State or national competent authority, as applicable, will check within 7 calendar days whether the proposed change can be considered a minor variation of Type IB, and whether the notification is correct and complete ('validation') before the start of the evaluation procedure.

When the proposed variation is not considered a minor variation of Type IB following the Annex to these guidelines, including any updated electronic version of these guidelines, 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 reference Member State or the national competent authority (as relevant) is of the opinion that it may have a significant impact on the quality, safety or efficacy of

the medicinal product, the holder and the concerned Member States, if applicable, will be informed immediately.

The holder will be requested to revise its application and to complete it in accordance with the requirements for a major variation of Type II application. Following receipt of the valid revised variation application, a Type II assessment procedure will be initiated (see section 2.3.2).

When the reference Member State or the national competent authority (as relevant) 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 of the procedure.

Within 30 days following the acknowledgement of receipt of a valid notification, the competent authority will notify the holder of the outcome of the procedure. If the competent authority 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.

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.

Within 30 days of receipt of the amended notification, the competent authority will inform the holder of its final acceptance or rejection of the variation(s) (including the grounds for the unfavourable outcome). Concerned Member States will be informed accordingly, when applicable.

Where a group of minor variations were submitted as part of one notification, the competent authority will inform the holder and the concerned Member States which variation(s) have been accepted or rejected following its review. The holder may withdraw single variations from the grouped application during the procedure (prior to the finalisation of the review by the competent authority).

Where necessary, the relevant authorities will update the marketing authorisation within 6 months following closure of the procedure. However, the accepted minor variations of Type IB variation may be implemented without awaiting the update of the marketing authorisation.

2.2.3. Type IB variations review for centralised procedure

Upon receipt of a Type IB notification, the Agency will handle the notification as follows:

The Agency will check within 7 calendar days whether the proposed change can be considered a minor variation of Type IB, and whether the notification is correct and complete (‘validation’) before the start of the evaluation procedure.

When the proposed variation is not considered a minor variation of Type IB following the Annex to these guidelines, including any updated electronic version of these guidelines, 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 Agency is of the opinion that it may have a significant impact on the quality, safety or efficacy of the medicinal product, the holder will be requested to revise its application and to complete it in accordance with the requirements for a major variation of Type II application. Following receipt of the valid revised variation application, a Type II assessment procedure will be initiated (see section 2.3.5).

When the Agency 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.

The rapporteur will be involved in the review of the Type IB notification.

Within 30 days following the acknowledgement of receipt of a valid notification, the Agency will notify the holder of the outcome of the procedure. If the Agency 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.

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 notification will be rejected.

Within 30 days of receipt of the amended notification, the Agency will inform the holder of its final acceptance or rejection of the variation(s) (including the grounds for the unfavourable outcome).Where a group of minor variations are submitted as part of one notification, the Agency will clearly inform the holder which variation(s) have been accepted or rejected following its review.

Where the opinion of the Agency is positive and the variation(s) affect(s) the terms of the Commission decision granting the marketing authorisation, the Agency will inform the Commission accordingly and transmit the relevant documentation. Where necessary, the Commission will update the marketing authorisation at the latest within 12 months. However, the accepted minor variation(s) of Type IB may be implemented without awaiting the update of the Commission decision granting the marketing authorisation and the agreed change(s) will be included in the annexes of any ongoing or subsequent Regulatory Procedure triggering the need to issue a Commission Decision.

2.3. Major variations of Type II

Hereby guidance is provided on the application of Articles 7, 10, 11, 13, 13c, 13d, 13e, 16, 17, 23 and 24 of the Variations Regulation to major variations of Type II.

The Variations Regulation and the Annex to these guidelines set out a list of changes to be considered as major variations of Type II. Such major variations require approval by the relevant competent authority before implementation.

2.3.1. Submission of Type II applications

Applications for major variations of Type II must be submitted by the holder simultaneously to all Member States concerned, to the national competent authority or to the Agency (as appropriate).

Holders may group under a single application 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 reference Member State, the national competent, authority or the Agency (as appropriate).

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 in a single Member State, or one or more major variation(s) of Type II with other minor variations affecting several marketing authorisations in a single Member State, provided that (i) the variations are the same for all the marketing authorisations concerned, (ii) the variations are submitted at the same time to the national competent authority, and (iii) the national competent authority has previously agreed to the grouping.

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

must submit these variations as one application for ‘worksharing’ (see section 3 on ‘worksharing’). If a submission has been made as one or several variations but not including all affected marketing authorisations owned by the same holder in one application for ‘worksharing’, the holder will be informed and requested to revise its application.

2.3.2. Type II variations assessment for mutual recognition and purely national procedures

Upon receipt of a Type II application, the reference Member State or national competent authority, as applicable, will handle the application as follows:

If the application has been submitted simultaneously to all the Member States concerned (when applicable) and contains the elements listed in Annex IV of the Variations Regulations and point 2., the competent authority will acknowledge receipt of a valid application of a major variation of Type II. The holder and the concerned Member States (when applicable) will be informed of the timetable at the start of the procedure.

In the mutual recognition procedure, 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. The concerned Member States will send to the reference Member State their comments within the deadlines set out in the timetable.

Within the evaluation period, the reference Member State or national competent authority, as applicable, may request the marketing authorisation holder to provide supplementary information, in which case the procedure will be suspended until the receipt of the supplementary information..

2.3.3. Outcome of Type II variations assessment for mutual recognition procedure

The reference Member State will finalise (after receipt of the holder’s response to the request for supplementary information, if applicable) and submit the assessment report and its decision on the application to the holder and the concerned Member States.

Within 30 days following receipt of the assessment report and the decision, the concerned Member States will recognise the decision and inform the reference Member State accordingly, unless a potential serious risk to public health or a potential serious risk to human health is identified that prevents a Member State from recognising the decision of the reference Member State. The Member State that, within 30 days following receipt of the assessment report and the decision of the reference Member State, identifies such a potential serious risk must inform the reference Member State and give a detailed statement of the reasons for its position.

The reference Member State will then refer the application to the corresponding coordination group for application of Article 29(3), (4) and (5) of Directive 2001/83/EC to the matter of disagreement and will inform the holder and the concerned Member States accordingly. The holder is not entitled to trigger a referral.

Where an application concerning a grouping of variations that includes at least a variation Type II is referred to the coordination group, the decision on the variations not subject to the referral will be suspended until the referral procedure has concluded (including, where relevant, the referral to the EMA relevant Committee under Articles 32 to 34 of Directive 2001/83/EC. However, only the variation(s) in respect of which a potential serious risk to human health has been identified will be discussed by the coordination group and eventually by the Committee, not the whole group.

The reference Member State will inform the concerned Member States and the holder about the approval or rejection of the variation(s) (including the grounds for the unfavourable outcome). Where several Type II variations, or a group of Type II variation(s) with other minor variations have been submitted as one application, the reference Member State will inform the holder and the concerned Member States which variation(s) have been accepted or rejected. The holder may withdraw single variations from the grouped application during the procedure (prior to the finalisation of the assessment of the reference Member State).

After approval of the variation(s), the competent authorities of the Member States concerned 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 Member States concerned.

The accepted major variation(s) of Type II can be implemented 30 days after the holder has been informed about the acceptance of the variation(s) by the reference Member State, provided that the necessary documents to amend the marketing authorisation have been submitted to the Member State concerned. 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. However, the variations in the group not subject to the referral may be implemented if so indicated by the reference Member State.

2.3.4. Outcome of Type II variations assessment for purely national procedure

By the end of the evaluation period (after receipt of the holder's response to the request for supplementary information, if applicable), the national competent authority 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).

Where several Type II variations, or a group of Type II variation(s) with other minor variations have been submitted as one application, the national competent authority will inform the holder which variation(s) have been accepted or rejected. The holder may withdraw single variations from the grouped application during the procedure (prior to the finalisation of the assessment by the national competent authority).

After approval of the variation(s), the national competent authorities will, where necessary, amend the marketing authorisation(s) 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 national competent authority.

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 national competent authority, provided that the necessary documents to amend the marketing authorisation(s) have been submitted.

2.3.5. Type II variations assessment for centralised procedure

Upon receipt of a Type II application, the Agency will handle the application as follows:

If the application submitted to the Agency contains the elements listed in Annex IV of the Variations Regulation and point 2., the Agency will acknowledge receipt of a valid application of a major variation of Type II. The marketing authorisation holder will be informed of the adopted timetable at the start of the procedure.

Within the evaluation period, the Committee may request supplementary information.

The evaluation will be suspended until the receipt of the supplementary information.

Timelines for the Committee assessment of responses will depend on the complexity and amount of data to be provided to the marketing authorisation holder. Timetable for assessment can be found on the EMA website.

An oral explanation may be held at the request of the Committee or the holder, where appropriate.

2.3.6. Outcome of Type II variations assessment in centralised procedure

Upon adoption of an opinion, the Agency will inform the marketing authorisation holder within 15 days as to whether the opinion is favourable or unfavourable (including the grounds for the unfavourable outcome).

Where several Type II variations, or a group of Type II variation(s) with other minor variations have been submitted as one application, the Agency will issue an opinion reflecting the outcome of the procedure. Such opinion will also list any variations which are not considered approvable. The holder may withdraw single variations from the grouped application during the procedure (prior to the adoption of the opinion by the Agency).

The re-examination procedure set-out in Article 9(2) of Regulation (EC) No 726/2004 also applies to the opinions adopted for major variations of Type II applications.

Where the opinion of the Agency is favourable and the variation(s) affects the terms of the Commission decision 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.

Upon receipt of the opinion and the relevant information, the Commission will, where necessary, amend the marketing authorisation within 2 months in the cases lay down on Article 23(1a) of the Variations regulation:

In the case of other variations, the Commission will, where necessary, amend the decision granting the marketing authorisation at the latest within 12 months.

The approved major variation(s) of Type II requiring amendment of the Commission decision granting the marketing authorisation within 2 months may only be implemented once the holder has been informed by the Commission accordingly. Where amendment of the decision granting the marketing authorisation is not required within 2 months, or where the approved variation(s) does not affect the terms of the Commission decision granting the marketing authorisation, the variation(s) may be implemented once the holder has been informed by the Agency that its opinion is favourable.

Variations related to safety issues must be implemented without delay, within a time-frame agreed between the Commission and the holder.

2.4. Extensions

Annex I of the Variations Regulation sets out a list of changes to be considered as extensions. 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. The extension can either be granted as a new marketing authorisation or will be included in the initial marketing authorisation to which it relates.

2.4.1. Submission of Extensions applications

Extension applications must be submitted to all Member States concerned, to the national competent authority, or to the Agency (as appropriate).

Holders may group under a single application 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 reference Member State, the national competent, authority or the Agency (as appropriate).

2.5. Annual update for human influenza and human coronavirus vaccines

Hereby guidance is provided on the application of Articles 12, 13f and 18 of the Variations Regulation to the annual update of human influenza vaccines.

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.

Any other variations to human influenza vaccines follow the variation procedures foreseen in other sections of these Guidelines.

The 'fast track' procedure consists of two steps. 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). The second step concerns the assessment of additional data where necessary.

Marketing authorisation holders are advised to discuss the annual update submissions in advance with the reference Member State, the national competent authority or the Agency, as appropriate.

If relevant, an annual update procedure for human coronavirus vaccines will be introduced by the Agency. Such procedure shall only apply after an announcement published on the Agency's website.

It is possible to update human influenza and coronavirus vaccines outside the annual procedure; please contact in advance the relevant authority to discuss such application, the data package including Module 3 structure and its content and the timelines in advance.

In addition, a special urgent procedure is foreseen in Article 21 of the Variations Regulation for cases of a pandemic situation due to human influenza or human coronavirus recognised by the Commission, pursuant to Regulation (EU) 2022/2371 of the European Parliament and of the Council (please see section 2.5a).

2.5.1. Submission of variations applications for annual update of human influenza vaccines

Variations concerning changes to the active substance for the annual update of human influenza vaccines applications must be submitted to the reference Member State and to all concerned Member States, to the national competent authority or to the Agency (as appropriate).

2.5.2. Variations assessment for annual update of human influenza vaccines for mutual recognition procedure

Upon receipt of an application for the annual update, the reference Member State will handle the application as follows:

The reference Member State will acknowledge receipt of a valid application within 7 days and inform the holder and the Member States concerned of the start of the procedure.

The reference Member State will prepare an assessment report and a decision on the application. To this end, the reference Member State will consider first the administrative and quality data. As the reference Member State must sent the assessment and the draft Decision within the maximum deadline of 45 days foreseen in the Regulation, it is expected that, in order to allow for sufficient time for the assessment of additional data (notably clinical and stability data) where necessary, the reference Member State will typically conclude its assessment of the administrative and quality data within 30 days of the reception of a valid application.

The reference Member State may request the holder to submit additional information (notably clinical or stability data); in such a case, it will inform the concerned Member States. When a request for additional information is sent to the holder, the 45 days deadline is stopped until the requested information has been submitted by the holder.

The reference Member State will transmit its assessment report and draft Decision to the concerned Member States. Within 12 days from the reception date, the concerned Member States will adopt a decision accordingly and inform the holder and the reference Member State thereof.

2.5.3. Variations assessment for annual update of human influenza vaccines for purely national procedure

Upon receipt of an annual variation human influenza vaccines application, the national competent authority will handle the application as follows:

The national competent authority will acknowledge receipt of a valid application of an annual variation human influenza vaccine and inform the holder accordingly.

Within the evaluation period, the national competent authority 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.

Within 45 days from the receipt of a valid application, the national competent authority 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).

2.5.4. Variations assessment for annual update of human influenza vaccines in centralised procedure

Upon receipt of an annual variation human influenza vaccines application, the Agency will handle the application as follows:

The Agency will acknowledge receipt of a valid application of an annual variation human influenza vaccine within 7 days and inform the holder of the start of the procedure.

The EMA has a maximum of 55 days from the start of the procedure to assess the application. The EMA may request the holder to submit additional information (notably clinical or stability data); in such a case, the 55 days deadline is stopped until the requested information has been submitted by the holder.

Where necessary and based on the opinion from the Agency, the Commission will amend the decision granting the marketing authorisation.

2.6. Human vaccines to address a public health emergency in the Union

Annexes I and II enables the active substance(s)of authorised human influenza vaccines, coronavirus vaccines or any other human vaccine that has the potential to address a public health emergency in the Union to be updated.

Such changes are classified as type II variations.

Marketing authorisation holders are advised to discuss submission of such variation in advance with the Agency or, as applicable, the reference Member State or the national competent authority, to consider the appropriateness of the change to the active substance, taking into account the epidemiological situation, the urgency and the vaccination campaigns, the data package including Module 3 structure and the timelines.

Any other variation to those vaccines not directly linked with the changes to the active substance follows the variation procedures foreseen in other sections of this guideline. For coronavirus vaccines or any other human vaccine that has the potential to address a public health emergency in the Union, upon agreement of the relevant authorities, addition of active substance(s) under the same marketing authorisation may be allowed, resulting potentially in the co-existence of different versions (e.g. different serotypes, strains, antigens or coding sequences or combination of serotypes, strains, antigens, or coding sequences) of the vaccine.

Furthermore, in order to provide for appropriate differentiation which may help healthcare professionals and/or patients to prescribe/select the appropriate version of the vaccine and to facilitate traceability and pharmacovigilance monitoring, marketing authorisation holders should propose qualifiers/abbreviations as part of the invented name. Furthermore, differentiation in the packaging of the different versions of the vaccine will be paramount in case of co-existence.

In accordance with Article 21 of the Variation Regulation, during a public health emergency recognised by the Commission pursuant to Regulation (EU) 2022/2371 of the European Parliament and of the Council, the relevant authority may, where certain pharmaceutical, non-clinical or clinical data are missing, exceptionally and temporarily accept a variation to the terms of a marketing authorisation for a human vaccine pertaining to the pathogen causing the public health emergency.

2.7. Urgent Safety Restrictions

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’.

Urgent safety restrictions concern interim change(s) in the terms of the marketing authorisation due to new information having a bearing on the safe use of the medicinal product. These urgent changes must be subsequently introduced via a corresponding variation in the marketing authorisation.

The holder must immediately notify all Member States concerned, the national competent authority or the Agency (as appropriate) of the restrictions to be introduced.

If no objections have been raised by the relevant authority or the Agency (for centrally authorised medicinal products) within 24 hours following receipt of that information, the urgent safety restrictions are deemed accepted. They must be implemented within a time frame agreed between

the reference Member State, the national competent authority or the Agency (as appropriate) and the holder.

Urgent safety restrictions may also be imposed by the Commission (for centrally authorised medicinal products) or by the national competent authorities (for nationally authorised medicinal products) in the event of a risk to public health in the case of medicinal products for human use.

The corresponding variation application reflecting the urgent safety restrictions (whether requested by the holder or imposed by the Commission or the national competent authorities) must be submitted by the holder as soon as possible within 15 days.

2.8. Statement of compliance under the Paediatric Regulation

Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use [10] ('Paediatric Regulation') provides for rewards in case of the completion of a paediatric investigation plan and the inclusion of the results of the studies in the product information: :

—Under Article 36(1) of Regulation (EC) No 1901/2006, a supplementary protection certificate is entitled to a 6-month extension of the period referred to in 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').

—Under Article 37 of Regulation (EC) No 1901/2006, the holder of a marketing authorisation for an orphan medicinal product is entitled to an extension of the 10-year period referred to in Article 8(1) of Regulation (EC) No 141/2000 to 12 years under certain conditions, including the addition of the compliance statement to the marketing authorisation.

It follows that, for the purposes of benefiting from the rewards provided for under Articles 36 or 37 of the Paediatric Regulation, a variation to add the compliance statement in the marketing authorisation may be required.

Where a medicinal product has been authorised, Article 23a of the Variations Regulation foresees the procedure to add the compliance statement in the marketing authorisation once the requirements foreseen in the Paediatric Regulation have been complied with. Specifically, the compliance statement should be included in the context of a relevant a variation (e.g. submission of the results of PIP studies following the PIP completion) or an *ad hoc* variation to the relevant authority. After verification that all relevant conditions are met, the compliance statement is to be included by the relevant authority in the technical dossier of the marketing authorisation.

For the purposes of legal certainty, the relevant authority 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. In the case of marketing authorisations granted under the centralised procedure, the confirmation that the compliance statement has been included in the marketing authorisation will be issued by the European Medicines Agency.

3. PROCEDURAL GUIDANCE ON WORKSHARING

In accordance with Article 20 of the Variations Regulation a holder is required 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 reference Member State, the national competent authority or the Agency (as appropriate) 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) more than one mutual recognition marketing authorisation of the same holder; or

(iii) more than one centralised marketing authorisation of the same holder; or

(iv) one or several purely national marketing authorisation(s) and one or several centralised marketing authorisation(s) of the same holder; or

(v) one or several purely national marketing authorisation(s) and one or several mutual recognition marketing authorisation(s) of the same holder; or

(vi) one or several mutual recognition marketing authorisation(s) and one or several centralised marketing authorisation(s) of the same holder; or

(vii) 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.

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'), will examine the variation on behalf of the other concerned authorities.

In order to use 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. 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.

In justified cases agreed by the competent authorities of the Member States and the Agency, where applicable, a holder may choose to follow the worksharing procedure described in this section also where a minor variation of type IB or a major variation of type II, or a group of variations where at least one of the variations is a minor variation of type IB or a major variation of type II, that does not contain any extension relates to several marketing authorisations owned by several holders in more than one Member State.

3.1. Submission of variation(s) application under worksharing

A variation or group of variations presented for worksharing must be submitted as explained in sections 2. above and must be transmitted as one integrated submission package covering all variations for all medicinal products. This must include a common cover letter and electronic application form (eAF), together with separate supportive documentation for each medicinal product concerned and revised product information (if applicable) for each medicinal product concerned. This will allow the Agency 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.

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

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

When an upcoming worksharing procedure does not affect any centralised marketing authorisation, the holder will inform the competent authority of the Member State preferred as reference authority

in advance of submission of the worksharing application. The chosen authority will confirm its acceptance to act as reference authority to the holder and to the coordination group, which at its next meeting will confirm the reference authority, and, if applicable pursuant to the third subparagraph of Article 20(3) of the Variations Regulation, assign another relevant authority to assist the reference authority. If none of the competent authorities agree to act as reference authority, the coordination group will assign the reference authority.

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

The reference authority will acknowledge receipt of a valid application for worksharing. The holder and the Member States concerned will be informed of the timetable at the start of the procedure.

As a general rule, worksharing procedures will follow the assessment period of the highest type of variation included.

The reference authority will prepare a draft opinion according to the communicated timetable and will circulate it to the concerned Member States as well as to the holder for information. Concerned Member States will, when applicable send their comments within the deadlines set out in the timetable.

Within the evaluation period, the reference authority may request the marketing authorisation holder to provide supplementary information, in which case the procedure will be suspended until the receipt of the supplementary information.

3.3. Outcome of the worksharing assessment not involving medicinal products authorised under the centralised procedure

The reference authority will finalise (after receipt of the holder's responses to the request for supplementary information, if applicable) its opinion on the application and inform the concerned Member States and the holder.

In case of a favourable opinion, the list of variations that are not considered approvable should be attached in the Opinion (if applicable). In case of an unfavourable outcome, the grounds for the unfavourable outcome should be explained.

When applicable, the concerned Member States will recognise the opinion within 30 days following receipt of the opinion and inform the reference authority accordingly, unless a potential serious risk to public health is identified that prevents a Member State from recognising the opinion of the reference authority. The Member State that, within 30 days following receipt of the opinion of the reference authority, identifies such a potential serious risk should inform the reference authority and give a detailed statement of the reasons for its position.

The reference authority will then refer the application to the coordination group for application of 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. The holder is not entitled to trigger a referral.

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 under Articles 32 to 34 of Directive 2001/83/EC.

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 Commission decision (as applicable), the Member States concerned will amend the marketing authorisation(s) accordingly, provided that

the documents necessary for the amendment of the marketing authorisation have been submitted to the Member States concerned.

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

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. 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.

3.4. Worksharing assessment involving medicinal products authorised under the centralised procedure

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

The Agency will acknowledge receipt of a valid worksharing application. Immediately after acknowledging the receipt of a valid application, the Agency will start the procedure. The holder will be informed of the adopted timetable at the start of the procedure.

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

Within the evaluation period, the EMA may request supplementary information in which case the procedure will be suspended until the receipt of the supplementary information. An oral explanation to the Committee can be held at the request of the relevant Committee or the marketing authorisation holder, where appropriate.

3.5. Outcome of the worksharing assessment involving medicinal products authorised under the centralised procedure

By the end of the evaluation period, the Agency will adopt an opinion on the application, including the assessment report. The Agency will inform the holder and Member States concerned (if applicable). In case of disagreement with the opinion, holders may request a re-examination thereof in accordance with the procedure set out in Articles 9(2) of Regulation (EC) No 726/2004.

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.

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

Upon receipt of a favourable opinion by the Member States concerned or the Commission, the following steps apply:

—For medicinal products authorised under the mutual recognition procedure or decentralised or purely national procedures, the Member States concerned must approve the opinion, 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.

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.

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 (i) the documents necessary for the amendment of the marketing authorisation(s) have been submitted to the Member States concerned, and (ii) the application has not been the object of a referral.

—For centrally authorised products, the Commission will, where necessary and provided that the necessary documents to amend the marketing authorisation(s) have been submitted, amend the relevant authorisation(s) within 2 months in the cases lay down on Article 23(1a) of the Variations regulation.

In the case of other variations, the Commission will amend the decision granting the marketing authorisation at the latest within 12 months.

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.

Major variation(s) of Type II (and those minor variation(s) of Type IB grouped with the Type II variation), with the exception of variations that require the adoption of a Commission decision within 2 months, may be implemented 30 days after receipt of the favourable opinion from the Agency, provided that the necessary documents to amend the marketing authorisation(s) have been submitted.

4. ANNEX

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 and Vaccine Antigen Master Files.

Where reference has to be made to specific variations in this Annex, the variation in question should be quoted using the applicable elements of 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, etc.)

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

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

For each chapter this Annex contains:

—A list of variations which should be classified as minor variations of Type IA or major variations of Type II in accordance with the definitions of 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.

This Annex does not deal with the classification of extensions as they are exhaustively listed in Annex I of the Variations Regulation. All changes specified in Annex I of the Variations Regulation must be considered extensions of the marketing authorisations; any other change can not be classified as such.

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') under the same code, 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 holder considers that the changes may have a significant impact on the quality, safety or efficacy of the medicinal product.

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

For the purpose of this Annex 'test procedure' has the same meaning as 'analytical procedure'; 'limits' has the same meaning as 'acceptance criteria'. 'Specification parameter' means the quality attribute for which a test procedure and limits are set, e.g. assay, identity, water content. The addition or deletion of a specification parameter therefore includes its corresponding test method and limits.

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 holder 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.

With regard to the data package, the relevant supporting data for Type IB and Type II variations will depend on the specific nature of the change.

In case of a change in therapeutic indication, posology or maximum daily dose, a review of quality documentation should be performed. A justification should be provided, considering the impact of the changes on the quality documentation (e.g. the need to change impurity limits or warnings for excipients with known effect/ threshold).

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. In such cases updated product information has to be submitted as part of the application with the relevant translations. Mock-ups or specimens should be provided to the reference Member State, the national competent authority or the Agency, if applicable.

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. Holders are reminded that compliance with the updated monograph should be implemented within 6 months.

References in the Annex to monographs of the Ph. Eur. are only applicable to active substance and/or excipient monographs and/or general monographs, i.e. finished product monographs are exempted.

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

With reference to Part III 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. Therefore, Chapter D in this guideline provides a list of variations which are specific to such PMFs or VAMFs. Following review of these variations, any marketing authorisation concerned must be updated in accordance with Chapter B.V of this guideline. 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.

References in this Annex to changes to the marketing authorisation dossier mean addition, replacement or deletion, unless specifically indicated. 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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[1] OJ L 334, 12.12.2008, p. 7.
[2] OJ L 209, 4.8.2012, p. 4.
[3] OJ L 136, 30.4.2004, p. 1.
[4] OJ L 311, 28.11.2001, p. 1.
[5] OJ L 311, 28.11.2001, p. 67.
[7] OJ C 229, 22.7.1998, p. 4.
[10] OJ L 378, 27.12.2006, p. 1.

ANNEX

852 # A. ADMINISTRATIVE CHANGES

853 **A.1**

A. 1 Change in the (invented) name of the medicinal product		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	for Centrally Authorised products	1	1, 2	IAIN
b)	for Nationally Authorised Products		2	IB
Conditions				
1.	The check by the EMA on the acceptability of the new name has been finalised and was positive.			
Documentation				
1.	Copy of the EMA letter of acceptance of the new (invented) name.			
2.	Revised product information.			

854 **A.2**

A.2 Change in name of the active substance, excipient, medical device (part), or packaging component	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
	1	1, 2, 3	IAIN
Conditions			
1. The active substance/ excipient/ medical device/ packaging component must remain unchanged.			
Documentation			
1. For active substance and excipients, proof of acceptance by WHO or copy of the INN list. If applicable, proof that the change is in line with the Ph. Eur.. For herbal medicinal product, declaration that the name is in accordance with the guideline on declaration of herbal substances and herbal preparations in (traditional) herbal medicinal products. For medical devices, updated CE certificate or Declaration of Compliance, if available.			
2. Revised product information, as appropriate.			
3. Amendment of the relevant section(s) of the dossier.			

855 **A.3**

A.3 Change in ATC Code	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
	1	1, 2	IA
Conditions			
1. Change following granting of or amendment to ATC Code by WHO.			
Documentation			
1. Proof of acceptance (by WHO) or copy of the ATC Code list.			
2. Revised product information.			

856 **A.4**

A.4 Change in the name and/or address of the marketing authorisation holder, ASMF holder, manufacturing site for an active substance, intermediate or finished product, primary and/or secondary packaging site, manufacturer responsible for batch release, site where quality control takes place, and/or supplier of a packaging component, medical device (part), starting material, reagent and/or excipient (when mentioned in the dossier)	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a) The change in the name and/or address concerns the marketing authorisation holder	2	1, 2	IAIN
b) The change in the name and/or address concerns a manufacturer(s)whose activities include batch release	1	1, 2	IAIN
c) The change in the name and/or address does not concern a manufacturer(s) whose activities include batch release nor the marketing authorisation holder	1	1, 2, 3	IA
Conditions			
1. The physical location of the concerned manufacturing site and all manufacturing operations must remain the same.			
2. The marketing authorisation holder must remain the same legal entity.			
Documentation			
1. 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, or a copy of the modified manufacturing authorisation, if available.			
2. Amendment of the relevant section(s) of the dossier, including revised product information as appropriate			
3. In case of change in the name of the holder of the Active Substance Master File, updated "letter of access".			

857 **A.5**

A.5 Deletion of manufacturing sites for an active substance, intermediate or finished product, primary and/or secondary packaging site, manufacturer responsible for batch release, site where quality control takes place, and/or supplier of a packaging component, medical device (part), starting material, reagent and/or excipient (when mentioned in the dossier)	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
	1,2	1	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. Amendment of the relevant section(s) of the dossier, including revised product information as appropriate.			

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B. QUALITY CHANGES

B.I ACTIVE SUBSTANCE

B.I.a) Manufacture

B.I.a.1

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		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
Manufacturer of an active substance or starting material or reagent or intermediate				
a)	Addition or replacement of a site responsible for manufacturing of an active substance or intermediate	1, 2, 3	1, 2, 3, 4, 5, 6	IA_{IN}
b)	Addition or replacement of a manufacturer of an active substance or intermediate that requires significant update to the relevant active substance section of the dossier, e.g. where a substantially different route of synthesis or manufacturing conditions is used, 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
c)	Addition or replacement of a site responsible for manufacturing of a starting material used in the manufacture of the active substance	1, 2, 3	1, 2, 3, 4, 5, 6	IA
d)	Addition or replacement of a site responsible for manufacturing of - a biological active substance or - a biological starting material /reagent/intermediate used in the manufacture of a biological active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product or - a material for which an assessment is required of viral safety and/or TSE risk			II
e)	Addition or replacement of a new herbal starting material supplier or of a new herbal active substance manufacturer using the same or different plant production (i.e. cultivated or wild collection)		1, 2, 4, 5, 6, 7, 8	IB
f)	Addition of a manufacturer of the active substance that is supported by an ASMF			II
g)	Addition or replacement of a manufacturing site responsible for sterilisation of the active substance using a Ph. Eur. method		1, 2, 4, 9	IB
h)	Addition or replacement of a manufacturing site responsible for micronisation of the active substance	2, 5	1, 4, 5	IA
Quality control testing arrangements for the active substance or starting material or intermediate				
i)	Addition or replacement of a site where batch control/testing of the active substance or starting material or intermediate takes place, applying a biological/immunological/immunochemical analytical procedure for a biological active substance (without change to the analytical procedures)		1, 9, 10	IB
j)	Addition or replacement of a site where batch control/testing takes place applying physicochemical and/or microbiological analytical procedures for the active substance or starting material or intermediate, if mentioned in the dossier	4, 6	1	IA
Other				
k)	Addition or replacement of a site responsible for storage of the Master Cell Bank and/or Working Cell Banks	7	1	IA

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 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 procedure remain the same.
6.	The analytical procedure is not a biological/immunological/immunochemical procedure.
7.	For Master Cell Bank and/or Working Cell Banks the storage conditions are identical to those already approved.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD), if applicable.
2.	A declaration from the marketing authorisation holder (and the ASMF holder, where applicable) that the synthetic 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 are the same as those already approved. For herbal active substances, a declaration that the geographical source, production of the herbal starting material/herbal substance and the manufacturing process of the herbal active substance 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 competent authority 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. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).
4.	Batch analysis data (in a comparative tabular format) for at least two batches (minimum pilot scale) [or 3 batches (unless otherwise justified) for biologicals] of the active substance from the current and proposed manufacturers/sites.
5.	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.
6.	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 analytical procedures of the active substance.
7.	For herbal starting material, a detailed comparison regarding specifications and critical quality attributes of the herbal starting material. For herbal active substance, a detailed comparison regarding specifications and critical quality attributes (e.g. for extracts: reference to the herbal starting material (incl. scientific binominal name and plant part), physical state, extraction solvent (nature and concentration), drug extract ratio (DER) and manufacturing process (including a stepwise comparison of all manufacturing steps in tabular format).

8.	For herbal starting material supplier, a GACP declaration from the new supplier (and updated QP declaration if the new supplier is also involved in the herbal active substance manufacture).
9.	Proof that the proposed site is appropriately authorised for the manufacturing operation concerned, i.e. for sterilisation of active substance. 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) or other relevant agreement 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.
10.	The analytical procedure transfer protocols in accordance with Eudralex Volume 4 Chapter 6 article 6.39 (which pre-define the acceptance criteria), from the old site to the new site (or new test laboratory). Depending on the variability of the specific method and the potential risk, to the quality, safety or efficacy of the product, posed by the proposed change, additional data such as a summary of the analytical procedure transfer test results may be required.

864 **B.I.a.2**

B.I.a.2 Change in the manufacturing process of the active substance		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Minor change in the manufacturing process of the active substance	1, 2, 3, 4	1, 2, 3, 6	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)	Change in the geographical source of a herbal starting material and /or production of a herbal substance		1, 2, 3, 5, 6	IB
d)	Minor change to the restricted part of an Active Substance Master File		1, 2, 3, 4	IB
e)	Deletion of a manufacturing process of the active substance	5, 6,	1	IA
Conditions				
1.	No adverse change in qualitative and quantitative impurity profile or in physico-chemical properties.			
2.	For chemical active substance: 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. For herbal active substances: the geographical source, production of the herbal starting material/herbal substance and the manufacturing process of the herbal active substance remain the same. For biological active substance/starting material/intermediate/reagent: the manufacturing steps remain the same and there are no changes to the manufacturing parameters (critical and non-critical PPs and IPCs) or to the specifications of the starting materials, intermediates, or active substance. There are no changes to the finished product. For all: there are no changes to the finished product.			
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.	There should at least remain one manufacturing process, as previously authorised.			
6.	The deletion should not be due to critical deficiencies concerning manufacturing.			
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), [or 3 batches (unless otherwise justified) for biologicals] 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 and the ASMF Holder 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.
5.	In the case of herbal starting materials, an updated GACP declaration and a declaration from the marketing authorisation holder that the manufacturing process of the herbal active substance remains the same.
6.	A declaration from the marketing authorisation holder that a full evaluation has been performed and the minor changes do not impact the quality, safety or efficacy of the active substance /medicinal product (e.g. minor amendments to process description without actual process change, such as details of reagents (e.g. buffers, media preparation). For herbal starting materials/active substances, this evaluation should include a detailed comparison regarding quality determining process characteristics.
	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.

865 **B.I.a.3**

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**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	An increase to the originally approved batch size	1, 2, 3, 4, 6, 7	1, 2, 4	IA
b)	Downscaling of the approved batch size	1, 2, 3, 4, 5	1, 2, 4	IA
c)	The change in batch size of a biological active substance/intermediate requires assessment of the comparability			II
d)	The scale for a biological active substance/intermediate is increased / decreased without process change (e.g. duplication of line)		1, 2, 3, , 5	IB
Conditions				
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 active substance is not a biological substance (refer to category c or d).			
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 and the control strategy for impurities has been reviewed and remains appropriate.			
7.	The active substance is not sterile.			
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 two production batches of the active substance or intermediate as appropriate, manufactured to both the currently approved and the proposed sizes. Batch analysis data of 3 batches (unless otherwise justified) for biological active substance, should be available for the proposed batch size.
3.	Copy of approved specifications of the active substance (and of the intermediate, if applicable).
4.	A declaration from the marketing authorisation holder (and 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.
5.	For biological active substance, a justification that an assessment of comparability is not required.

866 **B.I.a.4**

B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Tightening of in-process limits	1, 2, 3, 4	1, 2	IA
b)	Addition of new in-process test and limits with its corresponding analytical procedure	1, 2, 5	1, 2, 3, 4, 6	IA
c)	Deletion of a non-significant or obsolete 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)	Minor change of an analytical procedure for an in-process test	2, 4, 6, 8	1	IA
g)	Replacement of an in-process test		1, 2, 3, 4, 6	IB
Conditions				
1.	The change is not a consequence of any commitment from previous assessments to review in-process test 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, and is not as a result of a safety or quality issue , e.g. new unqualified impurity detected, or a change in total impurity limits.			
3.	Any change should be within the range of currently approved limits.			
4.	The analytical procedure remains the same, or changes in the analytical procedure are minor (e.g. a change in column length or temperature could be allowed, but not a different type of column or method).			
5.	Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.			
6.	The new analytical procedure is not a biological/immunological/immunochemical procedure. .			
7.	The in-process test does not concern a critical attribute, for example: • assay, • purity, • impurities (except when a solvent is no longer used in the manufacture of the active substance),			

	• a critical physical characteristic (for example: particle size, bulk or tapped density), • identity test, • or water content.
8.	Appropriate studies have been performed in accordance with the relevant guidelines and show that the updated analytical procedure is at least equivalent to the former analytical procedure.
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 (unless otherwise justified) for biologicals] of the active substance for all specification parameters.
5.	Justification/risk assessment from the marketing authorisation holder or the ASMF Holder, as appropriate, that the 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.
(*)	*Note:* *This variation category is not intended to include changes in relation to revisions of the control strategy with an intention to minimise redundant testing of parameters and attributes (critical or non-critical) that are tested at different stages during the production, or cases where process/ product characterisation performed after authorisation has shown that the attribute/ parameter is non-critical. Such changes require regulatory assessment and are to be handled as Type IB or II variations as appropriate.*

867 **B.I.a.5**

B.I.a.5	**Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Replacement of the strain(s) in a seasonal, pre-pandemic or a pandemic vaccine against human influenza			II

868 **B.I.a.6**

B.I.a.6	**Changes to the active substance of a vaccine against human coronavirus or other vaccine that has the potential to address a public health emergency in the Union**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Replacement or, upon agreement of the relevant authorities, addition of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine or other vaccine that has the potential to address a public health emergency in the Union			II
b)	Deletion of a serotype, strain, antigen or coding sequence or combination of serotypes, strains, antigens or coding sequences for a human coronavirus vaccine or other vaccine that has the potential to address a public health emergency in the Union		1, 2, 3	IB
Documentation				
1. Declaration that the remaining product presentation(s) are adequate for the dosing instructions and duration as mentioned in the summary of product characteristics, and the deletion has been agreed in principle with the Agency.				
2. Revised product information				
3. Declaration that the deletion of the serotype, strain, antigen or coding sequence is no longer appropriate in relation to the epidemiological evolution of the human virus of concern				

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

870 **B.I.b.1**

	B.I.b.1 Change in the specification attribute and/or acceptance criteria of an active substance, starting material/reagent/intermediate/ used in the manufacturing process of the active substance	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Change within the approved specification acceptance criteria for medicinal products subject to Official Control Authority Batch Release	1, 2, 3, 4	1, 2	IA_{IN}
b)	Change within the approved specification acceptance criteria	1, 2, 3, 4	1, 2	IA
c)	Addition of a new specification attribute with its corresponding analytical procedure	1, 2, 5, 6	1, 2, 3, 4, 5, 7	IA
d)	Deletion of a non-significant or an obsolete) specification attribute (*)	1, 2, 7	1, 2, 6	IA
e)	Deletion of a specification attribute which may have a significant effect on the overall quality of the active substance and/or the finished product			II
f)	Change outside of the approved specification acceptance criteria for the active substance			II
g)	Change outside of the approved specification acceptance criteria for starting material/reagent/intermediate which may have a significant effect on the overall quality of the active substance and/or the finished product			II
h)	Change outside of the approved specification acceptance criteria for starting material/reagent/intermediate		1, 2, 4 7	IB
i)	Change in specfication attribute for the active substance from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State		1, 2, 3, 4, 5, 7	IB
j)	Change of the analytical marker or widening of the acceptance criteria of the analytical marker (other extracts) for a herbal active substance.		1, 2, 3, 4, 7	IB
k)	Change in the testing of specification attribute, from routine to non-routine testing (skip or periodic testing)		1, 2, 8	IB
l)	Replacement of a specification attribute with its corresponding analytical procedure		1, 2, 3, 4, 5	IB
Conditions				
1.	The change is not a consequence of any commitment from previous assessments to review specification acceptance criteria (e.g. made during the procedure for the marketing authorisation application or a Type II variation procedure).			
2.	The change does not result from unexpected events arising during manufacture and is not as a result of a safety or quality issue, e.g. new unqualified impurity; change in total impurity limits.			
3.	Any change should be within the range of currently approvedacceptance criteria.			
4.	The analytical procedure remains the same, or changes in the analytical procedure are minor.			
5.	Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.			
6.	For any material, the change does not concern a genotoxic impurity (including nitrosamines). 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.
7.	The specification attribute does not concern a critical attribute, for example: • assay, • purity, • impurities (except when a solvent is no longer used in the manufacture of the active substance), • a critical physical characteristics (for example: particle size, bulk or tapped density), • identity test, • or water content. •
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 procedure and validation data, where relevant.
4.	Batch analysis data on two production batches [3 production batches (unless otherwise justified) for biologicals]) of the relevant substance for all specification attributes.
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 specification attribute is non-significant, or that the specification attribute is obsolete.
7.	Justification from the MAH or ASMF Holder as appropriate of the new specification attribute and the acceptance criteria.
8.	Justification from the MAH (or the ASMF holder) for the change in the testing of specification attribute, from routine testing to skip or periodic testing supported by analytical data as foreseen by relevant guidelines.
(*)	*Note:* *This variation category is not intended to include changes in relation to revisions of the control strategy with an intention to minimise redundant testing of parameters and attributes (critical or non-critical) that are tested at different stages during the production, or cases where process/ product characterisation performed after authorisation has shown that the attribute/ parameter is non-critical. Such changes require regulatory assessment and are to be handled as Type IB or II variations as appropriate.*

871 **B.I.b.2**

B.I.b.2 Change to analytical procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
Change to analytical procedure for the active substance				
a)	Minor change to an analytical procedure for the active substance	1, 2, 3	1, 2	IA
b)	Deletion of an analytical procedure for the active substance, substance if an alternative procedure is already authorised	6	1	IA
c)	Introduction, replacement or substantial change to a biological/immunological/immunochemical analytical procedure for an active substance			II
d)	Other change to an analytical procedure (including replacement or addition) for the active substance	1, 2, 3, 5, 6	1, 2	IB
Change to analytical procedure for starting material//reagent/intermediate used in the manufacturing process of the active substance				

e)	Minor change to an analytical procedure for starting material//reagent/ intermediate	1, 2, 3	1, 2	IA
f)	Deletion of an analytical procedure for a starting material/reagent/intermediate, if an alternative analytical procedure is already authorised	6	1	IA
g)	Introduction, replacement or substantial change to a biological/immunological/immunochemical analytical procedure for starting material /reagent /intermediate, used in the manufacturing process of an active substance		1, 2	IB
h)	Other change to an analytical procedure (including replacement or addition) for a starting material/ reagent/intermediate	1, 2, 3, 4, 5	1, 2	IA
Conditions				
1.	Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated analytical 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 analytical procedure is not a biological/immunological/immunochemical procedure.			
5.	Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.			
6.	An alternative analytical 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 analytical procedure and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new analytical procedure unless the new analytical procedure is added as an alternative procedure to a current one.			

872 **B.I.b.3**

B.I.b.3	**Change to an in-house reference standard/preparation for a biological active substance /finished product**	**Condition to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a)	Replacement of an in-house reference standard/preparation not covered by an approved qualification protocol (1)			II
b)	Replacement of an in-house reference standard/preparation not covered by an approved qualification protocol, where comparability test results using current and proposed reference standard/preparation material are available.		1, 2	IB
c)	Introduction of a qualification protocol for the preparation/replacement of an in-house reference standard/preparation (2)			II
d)	Substantial change to the qualification protocol for the preparation/replacement of an in-house reference standard or preparation which may have a significant impact on the quality, safety or efficacy of the active substance/finished product			II
e)	Other change to the qualification protocol for the replacement of an in-house reference standard or preparation		1	IB

f)	Extension of a re-test period/storage period of the in-house reference standard/preparation by real time data fully in line with the stability protocol		1, 3, 4	IB
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including a description of the manufacturing and qualification of the new in-house reference standard.			
2.	Comparative test results, showing that the current in-house reference standard and the proposed one are equivalent.			
3.	Confirmation that stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.			
4.	Copy of approved specifications.			
	(1) Note: Other changes to or with respect to an in-house reference standards /preparations, not covered by an approved protocol, should be classified in analogy to respective changes affecting the biological active substance/finished product. *(2) Note: Upon approval of the variation for the qualification protocol, the introduction of a new reference standard for a biological active substance/finished product according to the approved qualification protocol will be covered by the existing quality assurance system and hence, there will be no need to file a variation.*			

873 ***B.I.c) Container closure system***

874 **B.I.c.1**

B.I.c.1	**Change in immediate packaging of the active substance**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Change in immediate packaging of the active substance	1, 2, 3	1, 2, 3, 4, 6	IA
b)	Change in immediate packaging of sterile liquid active substance			II
c)	Change in immediate packaging of non-sterile liquid active substance		1, 2, 3, 5, 6	IB
d)	Deletion of one of the authorised bulk or final containers	4	1	IA
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.	The active substance is not a sterile active substance, liquid active substance or biological active substance.			
4.	The remaining packaging must be adequate for the storage of the bulk or final active substance at the authorised conditions.			
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 O_2, CO_2 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 foodstuffs.			
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 foodstuffs.
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 3 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.

875 **B.I.c.2**

B.I.c.2	**Change in the specification attribute and/or acceptance criteria of the immediate packaging of the active substance**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Tightening of specification acceptance criteria	1, 2, 3, 4	1, 2	IA
b)	Addition of a new specification attribute to the specification with its corresponding analytical procedure	1, 2, 5	1, 2, 3, 5,	IA
c)	Deletion of a non-significant or obsolete specification attribute (*)	1, 2	1, 2, , 4	IA
d)	Replacement of a specification attribute with its corresponding analytical procedure		1, 2, 3,	IB
Conditions				
1.	The change is not a consequence of any commitment from previous assessments to review specification acceptance criteria (e.g. made during the procedure for the marketing 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, and is not as a result of a saftery or quality issue.			
3.	Any change should be within the range of currently approved acceptance criteria.			
4.	The analytical procedure remains the same, or changes in the analytical procedure are minor			
5.	Any new analytical procedure 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 procedure and validation data, where relevant.			
4.	Justification/risk assessment from the marketing authorisation holder or the ASMF Holder, as appropriate, that the specification attribute are non-significant, or that the specification attribute is obsolete.			
5.	Justification from the marketing authorisation holder or the ASMF Holder, as appropriate, of the new specification attribute and the acceptance criteria.			
(*)	*Note:* *This variation category is not intended to include changes in relation to revisions of the control strategy with an intention to minimise redundant testing of parameters and attributes (critical or non-critical) that are tested at different stages during the production, or cases where process/ product characterisation performed after authorisation has shown that the attribute/ parameter is*			

non-critical. Such changes require regulatory assessment and are to be handled as Type IB or II variations as appropriate.

876 **B.I.c.3**

B.I.c.3	**Change in analytical procedure for the immediate packaging of the active substance**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Minor change to an approved analytical procedure	1, 2, 3	1, 2	IA
b)	Other change to an analytical procedure (including replacement or addition)	1, 3,	1, 2	IA
c)	Deletion of an analytical procedure if an alternative 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 analytical procedure is at least equivalent to the former procedure.			
2.	The analytical procedure 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 analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.			
.				
4.	There is still a analytical procedure registered for the specification attribute 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 analytical procedure and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new analytical procedure.			

877 **B.I.c.4**

B.I.c.4	**Change of a secondary packaging component of the active substance (including replacement or addition), when mentioned in the dossier**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
		1, 2, 3, 4	1	IA
Conditions				
1.	The secondary packaging does not play a functional role on the stability of the active substance, or if it does, it is not less protective than the approved one.			
2.	The changed packaging component must be adequate for the storage of the active substance at the authorised conditions.			
3.	The change should not be due to critical deficiencies of the former packaging component.			
4.	The change is not a result of any unexpected events arising during manufacture or storage of the active substance.			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

878 ***B.I.d) Stability***

879 **B.I.d.1**

B.I.d.1	**Change in the re-test period/storage period or storage conditions of the active substance**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**

a)	Re-test period/storage period			
1.	Reduction of re-test period/storage period of the active substance	1	1, 2, 3	IA
2	Introduction of re-test period/storage period of the active substance		1, 2, 3	IB
3.	Extension of the retest period/storage period of the active substance based on extrapolation not in accordance with relevant stability guidelines or based on stability modelling			II
4.	Extension of re-test period/storage period of the active substance supported by real time data not in accordance with an approved stability protocol or an extension based on extrapolation of stability data in accordance with relevant stability guidelines		1, 3	IB
5.	Extension of a re-test period/storage period of the active substance supported by real time data fully in line with the stability protocol	3	1, 2, 3	IA
b)	Storage conditions			
1.	Change to more restrictive storage conditions of the active substance	1, 4	1, 2, 3	IA
2.	Change in storage conditions of the active substance		1, 2, 3	IB
c)	Change to an approved stability protocol of the active substance	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.			
3.	Stability studies have been performed in accordance with a currently approved stability protocol. Real time data are submitted. All batches meet their pre-defined specification at all time points. No trends have been observed.			
4.	The physical state of the active substance has not changed.			
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 [3 batches (unless otherwise justified) 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/ storage 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.			

880 ***B.I.e) Additional regulatory tools***

881 **B.I.e.1**

B.I.e.1	**Introduction of a new design space or extension of an approved design space for the active substance**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	New design space for one or more unit operations in the manufacturing process of the active substance including the resulting in-process controls and/or analytical procedures		1, 2, 3	II

b)	New design space (method operable design range (MODR)) for a test procedures for starting materials/reagents/ intermediates and/or the active substance		1, 2, 3	II
c)	Extension of an approved design space for the active substance and/or analytical procedures for starting materials/reagents/intermediates		1, 2, 3	IB
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 including risk assessment and multivariate studies or process modelling, as appropriate, demonstrating where relevant that a systematic understanding of how material attributes and process parameters impact the critical quality attributes of the active substance has been achieved.			
2.	Description of the design space in tabular format, and/or in the form of mathematical equation, as relevant, including the variables (material attributes and process parameters, as appropriate) with their proposed ranges and limits.			
3.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

882 **B.I.e.2**

B.I.e.2 Introduction of a post approval change management protocol related to the active substance		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. 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).			

883 **B.I.e.3**

B.I.e.3 Deletion of an approved change management protocol related to the active substance		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
		1	1, 2	IA
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).			

884 **B.I.e.4**

B.I.e.4 Changes to an approved change management protocol		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. 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 the changes do not change the overall strategy defined in the protocol and are not broader than the currently approvedprotocol.

885 **B.I.e.5**

B.I.e.5	**Implementation of changes foreseen in an approved change management protocol**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Implementation of changes foreseen in a PACMP via Type IA notification	1	1, 2, 4	IA
b)	Implementation of changes foreseen in a PACMP via Type IA_{IN} notification	2	1, 2, 3, 4	IA_{IN}
c)	Implementation of changes foreseen in a PACMP via Type IB notification		1, 2, 3, 4	IB
Conditions				
1.	The proposed change has been performed fully in line with the approved change management protocol which requires its notification within 12 months following implementation.			
2.	The proposed change has been performed fully in line with the approved change management protocol, which requires its immediate notification following implementation.			
Documentation				
1.	Reference to the approved change management protocol.			
2.	Declaration that the change is in accordance with the approved change management protocol and that the study results meet the acceptance criteria specified in the protocol. . *			
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).			
	Note: *In case the acceptance criteria and / or other conditions in the protocol are not met, the change cannot be implemented as a variation of this category and should instead be submitted as variation of the applicable category without PACMP.			

886 **B.I.e.6**

B.I.e.6	**Introduction of a product lifecycle management document related to the active substance**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
			1, 2, 3	II
Documentation				
1.	The content of the product lifecycle management document 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, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic understanding of how material attributes and process parameters impact the critical quality attributes of the active substance has been achieved.			
2.	The product lifecycle management document includes a description of the material attributes, quality attributes and process parameters (or analytical procedure parameters), their proposed limits and ranges, and future variation reporting categories, in a tabular format.			
3.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

887 **B.I.e.7**

B.I.e.7	**Changes to process parameters or quality attributes related to the active substance as described in a product lifecycle management document**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**

a) Major change to a process parameter or quality attribute		1, 2, 3	II
b) Minor change to a process parameter or quality attribute	1	1, 2, 3	IA
c) Minor change to a process parameter or quality attribute	2	1, 2, 3	IA_{IN}
d) Other changes to a process parameter or quality attribute		1, 2, 3	IB
Conditions			
1. The change has been foreseen in the product lifecycle management document as a Type IA variation requiring notification within 12 months following implementation			
2. The change has been foreseen in the product lifecycle management document as a Type IA variation requiring immediate notification following implementation			
Documentation			
1. A summary and justification of the proposed change(s), clearly describing the present and proposed situation and supporting documentation.			
2. An updated product lifecycle management document including updated description of the material attributes, quality attributes or process parameters (or analytical procedure parameters), as appropriate, their proposed limits and ranges, and future variation reporting categories, in tabular format.			
3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

B.II. FINISHED PRODUCT

B.II.a) Description and composition

B.II.a.1

B.II.a.1 Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking.	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a) Changes in imprints, bossing or other markings	1, 2, 3, 4	1	IA_{IN}
b) Changes in scoring/break lines intended to divide into equal doses		1, 2	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. Results of the appropriate Ph. Eur tests demonstrating equivalence in characteristics/correct dosing.			

B.II.a.2

B.II.a.2 Change in the shape or dimensions of the pharmaceutical form	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a) Immediate release tablets, capsules, suppositories and pessaries	1, 2, 3, 4	1, 4	IA_{IN}
b) Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses		1, 2, 3, 4	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 old one. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the new product compared to the old 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 guideline on Investigation of Bioequivalence). For herbal medicinal product comparative disintegration data may be acceptable.			
3.	Justification for not submitting a new bioequivalence study according to the relevant guideline on Investigation of Bioequivalence.			
4.	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.				

892 **B.II.a.3**

B.II.a.3 Change in the composition (excipients) of the finished product		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Change in components of the flavouring or colouring system			
1.	Addition, deletion or replacement	1, 2, 3, 4, 5, 6, 7, 9	1, 2, 4, 5,	IA_{IN}
2.	Increase or reduction	1, 2, 3, 4,	1, 2	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, 6	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 (including biological excipients or 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
3.	Change that is supported by a bioequivalence study			
4.	Replacement of excipient(s) with a comparable excipient(s) with the same functional characteristics		1, 3, 4, 5, 6, 7, 8	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 competent authorities 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. Regulation (EC) No 1333/2008 of the European Parliament and of the Council ([1]) and Commission Regulation (EU) No 231/2012 ([2]) on food additives and Regulation (EC) No 1334/200 ([3]) for flavours).
6.	Any new component does not include 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 old one (no significant differences regarding comparability, see the relevant guideline on Investigation of Bioequivalence. For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.
9.	The change is not the result of stability issues and/or should not result in potential safety concerns i.e. differentiation between strengths.
10.	The product concerned is not a biological medicinal product.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), and 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 competent authorities 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 competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
4.	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. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).
5.	Data to demonstrate that the new excipient does not interfere with the finished product specification analytical procedures, if appropriate.
6.	Justification for the change/choice of excipients etc. must be given by appropriate development pharmaceutics (including stability aspects and antimicrobial preservation where appropriate).
7.	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.

8.	Justification for not submitting a new bioequivalence study according to the current guideline on Investigation of Bioequivalence.
	([1]) OJ L 237, 10.9.1994, p. 13. *([2]) OJ L 6, 10.1.2009, p. 20.* *([3]) OJ L 184, 15.7.1988, p. 61.*

893 **B.II.a.4**

B.II.a.4 Change in coating weight of oral dosage forms or change in weight of capsule shells		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Solid oral pharmaceutical forms	1, 2, 3, 4	1, 2	IA
b)	Gastro-resistant pharmaceutical forms where the coating is a critical factor for the release mechanism		1, 3, 4, 5, 6	IB
c)	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 old one. For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.			
2.	The coating is not a critical factor for the release mechanism.			
3.	The 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 competent authorities 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 competent authorities 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.			
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 competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).			
4.	Comparative batch analysis data and comparative dissolution profile data of at least two pilot scale batches of the finished product in the current and proposed formulation.			
5.	Justification for not submitting a new bioequivalence study according to the current guideline on the Investigation of Bioequivalence.			
6.	Declaration that the finished product specification has only been updated in respect of weight and dimensions.			

894 **B.II.a.5**

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	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**

			II

895 **B.II.a.6**

B.II.a.6 Deletion of the solvent / diluent container from the pack	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. 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.			

896 ***B.II.b) Manufacture***

897 **B.II.b.1**

B.II.b.1 Change in the manufacturing site for part or all of the manufacturing process of the finished product (except for batch release and batch control testing sites)	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a) Addition or replacement of a site responsible for secondary packaging	1, 2	1, 7	IA_{IN}
b) Addition or replacement of a site responsible for primary packaging	1, 2, 3, 4	1, 2, 7, 8	IA_{IN}
c) Addition or replacement of a site responsible for any manufacturing operation(s) of pharmaceutical forms manufactured by complex manufacturing processes (*)			II
d) Addition or replacement of a site which requires an initial or product specific GMP inspection			II
e) Addition or replacement of a site responsible for any manufacturing operation(s) for non-sterile medicinal products and for sterile medicinal products (including those that are aseptically manufactured)		1, 2, 4, 5, 6, 7, 8	IB
f) Addition or replacement of a site responsible for the assembly of an integral medical device		1, 2, 3, 4, 7	IB
Conditions			
1. Satisfactory inspection in the last three years by an inspectorate of one of the Member States of the EU/EEA or for sites located in a country where an operational Good Manufacturing Practice (GMP) mutual recognition agreement (MRA) or other relevant agreement exists between the country concerned and the EU, by that concerned international partner authority.			
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.			
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)[17] 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 proof issued within the last 3 years by the relevant international authority. 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. Copy of approved release and end-of-shelf life specifications if relevant.			

4.	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). Batch analysis data of 3 batches (unless otherwise justified) of the biological finished product, manufactured from the current and proposed manufacturers/sites.
5.	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 appropiate imaging technique.
6.	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.
7.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).
8.	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 QP is at the disposal of a manufacturing authorisation holder according to Art. 41 of Directive 2001/83/EC and 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 46a ([1]) of Directive 2001/83/EC, manufacture 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.	
(*) Note: In change code B.II.b.1, a complex manufacturing processes is, amongst others, intended to cover situations where the link between quality characteristics and in-vivo performance is not fully understood. A complex manufacturing process could include the following scenarios (not exhaustive list); e.g. nanomedicines, ATMPs, liposomal formulations, lipid nanoparticles, continuous manufacturing, decentralised manufacturing, inhalation products. Where relevant, if a change is submitted as a type IB variation, it is up to the applicant to provide adequate justification for not considering a manufacturing process as a 'complex' one. However, under the safeguard clause, it should be noted that if the supplied justification is not accepted, it is possible for the competent authority to upgrade the submission to a type II variation. If unsure, applicants should consult the relevant competent authority before submitting the variation.	
[(1)] OJ L 33, 8.2.2003, p. 30.	

898

899 **B.II.b.2**

B.II.b.2 Change to , batch release arrangements and quality control testing of the finished product		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Addition or replacement of a site where batch control/testing takes place applying physicochemical and/or microbiological analytical procedures for the finished product	2, 3, 4, 5	1, 4	IA
b)	Addition or replacement of a site where batch control/testing takes place applying a biological/immunological/immunochemical analytical procedure for a biological finished product (without change to analytical procedures)		1, 4, 5	IB
c)	Addition or replacement of a site responsible for batch release			
1.	Not including batch control/testing	1, 2, 5	1, 2, 3, 4	IA_{IN}
2.	Including batch control/testing applying physicochemical and/or microbiological analytical procedures for the finished product	1, 2, 3, 4, 5	1, 2, 3, 4	IA_{IN}
3.	Including batch control/testing applying a biological/immunological/immunochemical analytical procedure for a biological finished product (without change to analytical procedures)		1, 4, 5	IB

Conditions	
1.	The manufacturer responsible for batch release must be located within the EU/EEA and hold a valid Manufacturing Authorisation for the proposed operations issued by the relevant competent authority of the EU/EEA Member State. 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 analytical procedure is not a biological/immunological /immunochemical procedure
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) or other relevant agreement 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. A reference to the EudraGMP database will suffice. For a manufacturing site outside the EU/EEA where an operational GMP mutual recognition agreement (MRA) or other relevant agreement exists between the country concerned and the EU: a valid proof of GMP compliance, 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.	For centralised procedure only: contact details of new contact person in the EU/EEA for product defects and recalls, if applicable.
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 format), including revised product information as appropriate.
5.	The analytical procedure transfer protocols in accordance with Eudralex Volume 4 Chapter 6 article 6.39 (which pre-define the acceptance criteria), from the old site to the new site (or new test laboratory). Depending on the variability of the specific method and the potential risk, to the quality, safety or efficacy of the product, posed by the proposed change, additional data such as a summary of the analytical procedure transfer test results may be required.

900 **B.II.b.3**

B.II.b.3	**Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Minor change in the manufacturing process	1, 2, 3, 4, 5, 6, 7	1, 2, 3, 4, 5, 6, 7, 8, 9	IA
b)	Substantial change to a manufacturing process of the finish product that may have a significant impact on the quality, safety and efficacy of the medicinal product			II
c)	Introduction of a non-standard terminal sterilisation method			II
d)	Introduction or increase in an overage that is used for the active substance			II
e)	Change in the holding time of an intermediate or bulk product used in the manufacture of the finished product a		1, 6, 10	IB

	Conditions
1.	No change in qualitative and quantitative impurity profile or in physico-chemical properties.
2.	The change relates to an immediate release solid oral dosage form / oral solution or the change relates to non-critical process parameter(s), i.e. 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 currently registered process has to be controlled by relevant in-process controls and no changes (widening or deletion of limits) are required to these controls.
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 competent authorities 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 Investigation of Bioequivalence.
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 1 batch [or 3 batches (unless otherwise justified) for biologicals,] manufactured to both the currently approved and the proposed process. Batch data on the next 2 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 competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
9.	A declaration from the marketing authorisation holder that a full evaluation has been performed and the minor change does not impact the quality, safety or efficacy of the medicinal product (e.g. minor amendments to process description without actual process change).
10.	Data to validate the proposed change in holding time and/or storage condition of the intermediate or bulk product (minimum of two batches at pilot or commercial scale). Qualitative and quantitative (if required) composition of the intermediate or bulk container should be described and its specification stated. If pilot scale batches are provided, a commitment to verify these data on commercial scale batches. Declaration that the finished product shelf-life is set in accordance with the *Note for guidance on start of shelf-life of the finished dosage form*, or otherwise justified.

901 **B.II.b.4**

B.II.b.4	**Change in the batch size (including batch size ranges) of the finished product**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Up to 10-fold increase compared to the originally approved batch size	1, 2, 3, 4, 5, 7	1, 3, 4	IA
b)	Downscaling down to 10-fold	1, 2, 3, 4, 5, 6	1, 3, 4	IA
c)	The change requires assessment of the comparability of a biological medicinal product or the change in batch size requires a new bioequivalence study			II
d)	The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes (*)			II
e)	More than 10-fold increase/decrease compared to the originally approved batch size		1, 2, 3, 4, 5, 6, 7	IB
f)	The scale for a biological medicinal product is increased / decreased without process change (e.g. duplication of line)		1, 2, 3, 4, 5, 6, 7	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 medicinal product (refer to category c or f).			
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 two production batches manufactured to both the currently approved and the proposed sizes. Batch analysis data of 3 batches (unless otherwise justified) for biological finished product should be available for the proposed batch size.
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 competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
7.	A justification that an assessment of comparability is not required.
	(*) Note: In change code B.II.b.4, 'complex manufacturing processes' is intended to cover situations where the actual manufacture of the finished product involves a process which includes one or more processing steps that may give rise to scale-up difficulties. A complex manufacturing process could include the following scenarios (not exhaustive list); e.g. nanomedicines, ATMPs, liposomal formulations, lipid nanoparticles, continuous manufacturing, decentralised manufacturing, inhalation products. Where relevant, if a change is submitted as a type IB variation, it is up to the applicant to provide adequate justification for not considering a manufacturing process as a 'complex' one. However, under the safeguard clause, it should be noted that if the supplied justification is not accepted, it is possible for the competent authority to upgrade the submission to a type II variation. If unsure, applicants should consult the relevant competent authority before submitting the variation.

902 **B.II.b.5**

	B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Minor changes of in-process limits	1, 2, 3, 4	1, 2	IA
b)	Addition of new in-process testand limits with its corresponding analytical procedure	1, 2, 5	1, 2, 3, 4, 5, 7	IA
c)	Deletion of a non-significant or obsolete 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 in-process test limits, which may have a significant effect on overall quality of the finished product			II
f)	Minor change of an analytical procedure for an in-process test	2, 4, 6, 8	1 8	IA
g)	Replacement of an in-process test		1, 2, 3, 4, 6	IB
	Conditions			
1.	The change is not a consequence of any commitment from previous assessments to review in-process test (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 and is not as a result of a safety or quality issue, e.g. new unqualified impurity detected, or a change in total impurity limits.			
3.	Any change should be within the range of currently approved limits.			
4.	The analytical procedure remains the same, or changes in the procedure are minor (e.g. a change in column length or temperature could be allowed, but not a different type of column or method).			

5.	Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
6.	The analytical procedure is not a biological/immunological/immunochemical procedure.
7.	The in-process test does not concern the control of a critical attributefor example: • assay, • purity, • impurities (except solvent is not longer used in the manufacture), • a critical physical characteristic (for example: particle size, bulk or tapped density…), • identity test (unless there is a suitable alternative control already present), • microbiological control (unless not required for the particular dosage form)
8.	Appropriate studies have been performed in accordance with the relevant guidelines to show that the updated analytical procedure is at least equivalent to the former analytical procedure
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 procedure and validation data, where relevant.
4.	Batch analysis data on two production batches [3 production batches (unless otherwise justified) for biologicals] 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.
8.	Comparative study results or comparative analysis results showing that the current analytical procedure and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new analytical procedure.
(*)	Note: This variation category is not intended to include changes in relation to revisions of the control strategy with an intention to minimise redundant testing of parameters and attributes (critical or non-critical) that are tested at different stages during the production, or cases where process/ product characterisation performed after authorisation has shown that the attribute/ parameter is non-critical. Such changes require regulatory assessment and are to be handled as Type IB or II variations as appropriate.

903 ***B.II.c) Control of excipients***

904 **B.II.c.1**

B.II.c.1	**Change in the specification attribute and/or acceptance criteria of an excipient**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Change within the approved specification acceptance criteria	1, 2, 3, 4	1, 2	IA
b)	Addition of a new specification attribute to the specification with its corresponding analytical procedure	1, 2, 5, , 6	1, 2, 3, 4, 5, 6, 8	IA
c)	Deletion of a non-significant or obsolete specification attribute	1, 2, 7	1, 2, 7	IA
d)	Change outside of the approved specification acceptance criteria			II
e)	Deletion of a specification attribute which may have a significant effect on the overall quality of the finished product			II
f)	Change in specification attribute for the excipient from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State		1, 2, 3, 4, 5, 6, 8	IB

g)	Replacement of a specification attribute with its corresponding analytical procedure		1, 2, 3, 4	IB
Conditions				
1.	The change is not a consequence of any commitment from previous assessments to review specification acceptance chriteria (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 and is not as a result of a safety or quality issue, e.g. new unqualified impurity; change in total impurity limits.			
3.	Any change should be within the range of currently approved acceptance chriteria.			
4.	The analytical procedure remains the same, or changes in the analytical procedure are minor.			
5.	Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.			
6.	The change does not concern a genotoxic impurity.			
7.	The specification attribute does not concern the control of a criticalattribute, for example: • assay, • purity, • impurities (except when a solvent is no longer used in the manufacture of the excipient), • a critical physical characteristics (for example: particle size, bulk or tapped density…) • identity test (unless there is a suitable alternative control already present), • water content • 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 procedure and validation data, where relevant.			
4.	Batch analysis data on two production batches [3 production batches (unless otherwise justified) 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 Guideline on The Investigation of Bioequivalence, if appropriate.			
7.	Justification/risk assessment showing that the attribute is non-significant or that it is obsolete.			
8.	Justification of the new specification attribute and the acceptance criteria.			
(*)	Note: This variation category is not intended to include changes in relation to revisions of the control strategy with an intention to minimise redundant testing of parameters and attributes (critical or non-critical) that are tested at different stages during the production, or cases where process/ product characterisation performed after authorisation has shown that the attribute/ parameter is non-critical. Such changes require regulatory assessment and are to be handled as Type IB or II variations as appropriate.			

905 **B.II.c.2**

B.II.c.2	**Change in analytical procedure for an excipient**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Minor change to an approved analytical procedure	1, 2, 3,	1, 2	IA
b)	Deletion of an analytical procedure if an alternative test procedure is already authorised	5	1	IA

c)	Introduction, replacement or substantial change to a biological/immunological/immunochemical analytical procedure for an excipient			II
d)	Other changes to a analytical 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 analytical procedure is at least equivalent to the former analytical procedure.			
2.	There have been no changes of the total impurity limits; no new unqualified impurities 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 analytical procedure is not a biological/immunological/immunochemical procedure .			
5.	An alternative analytical 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 analytical and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new analytical procedure.			

906 **B.II.c.3**

B.II.c.3 Change in source of an excipient or reagent with TSE risk		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	From TSE risk material to vegetable or synthetic origin			
1.	For excipients or reagents not used in the manufacture of a biological active substance or in a biological medicinal product	1	1	IA
2.	For excipients or reagents used in the manufacture of a biological active substance or in a biological medicinal product		1, 2	IB
b)	Change or introduction of a TSE risk material or replacement of a TSE risk material from a different TSE risk material, not covered by a 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.			

907 **B.II.c.4**

B.II.c.4 Change in synthesis, manufacturing or recovery of an excipient (when described in the dossier)		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Minor change in synthesis, manufacturing or recovery of an excipient	1, 2, 3	1, 2, 3, 4	IA
b)	Change in the manufacturing site, synthesis, manufacturing or recovery of the excipient which may affect the quality, safety or efficacy of the finished product			II
c)	Deletion of one manufacturing process of an excipient	4, 5	1	IA

d)	Addition or replacement of a site responsible for the manufacture or testing of an excipient where, required to be described in the dossier		1, 2	IB
Conditions				
1.	The synthetic route/manufacturing process 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.			
3.	The excipient is not a biological substance.			
4.	The deletion should not be due to critical deficiencies concerning manufacturing.			
5.	There should at least remain one manufacturing process, as previously authorised.			
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) [or 3 production batches (unless otherwise justified) for biological excipients] of the excipient manufactured according to the present and proposed process, or by the present and proposed manufacturer, as applicable.			
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.			

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

909 **B.II.d.1**

B.II.d.1 Change in the specification attribute and/or acceptance criteria of the finished product		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Change within the specifications acceptance criteria	1, 2, 3, 4	1, 2	IA
b)	Change within the specification acceptance criteria for medicinal products subject to Official Control Authority Batch Release	1, 2, 3, 4	1, 2	IA_{IN}
c)	Addition of a new specification attribute with its corresponding analytical procedure	1, 2, 5, 6	1, 2, 3, 4, 5, 7	IA
d)	Deletion of a non-significant or obsolete specification attribute (e.g. deletion of odour and taste or identification test for a colouring or flavouring material) ([1])	1, 2, 8	1, 2, 6	IA
e)	Change outside of the approved specification acceptance criteria of the finished product			II
f)	Deletion of a specification attribute which may have a significant effect on the overall quality of the finished product			II
g)	Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur ([2])	1, 2, 3, 4, 6, 7	1, 2	IA_{IN}
h)	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, 9	1, 2, 4	IA
i)	Change in the testing of specification attribute, from routine to non-routine testing (skip or periodic testing)		1, 2, 8	IB
j)	Replacement of a specification attribute with its corresponding analytical procedure		1, 2, 3, 4, 5, 7	IB

Conditions	
1.	The change is not a consequence of any commitment from previous assessments to review specification acceptance criteria (e.g. made during the procedure for the marketing 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 or as a result of a satefy or quality issue, e.g. new unqualified impurity; change in total impurity acceptance criteria.
3.	Any change should be within the range of currently approved acceptance criteria.
4.	The analytical procedure remains the same, or changes in the analytical procedure are minor.
5.	Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
6.	The change does not concern any impurities (including genotoxic) or dissolution.
7.	The change concerns the updating of the microbial control acceptance criteria to be in line with the current Pharmacopoeia, and the currently registered microbial control acceptance criteria (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.
8.	The specification parameter attribute or proposal for the specific dosage form does not concern a critical attribute, for example: • assay, • purity, • impurities (except solvent is not used in the manufacture of the finished product) • a critical physical characteristic (for example: 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.
9.	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 procedure and validation data, where relevant.
4.	Batch analysis data on two production batches [3 production batches (unless otherwise justified) for biologicals] 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 attribute is non-significant or that it is obsolete.
7.	Justification of the new specification attribute and the acceptance criteria
8.	Justification from the MAH for the change in the testing of specification attribute, from routine testing to skip or periodic testing supported by a sufficient amount of historical data compliant with the specification.
	(1) Note : *This variation category is not intended to include changes in relation to revisions of the control strategy with an intention to minimise redundant testing of parameters and attributes (critical or non-critical) that are tested at different stages during the production, or cases where process/ product characterisation performed after authorisation has shown that the attribute/ parameter is non-critical. Such changes require regulatory assessment and are to be handled as Type IB or II variations as appropriate.*
	(2) Note: *There is no need to notify the competent authorities of an updated general 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.

910 **B.II.d.2**

B.II.d.2 Change to analytical procedures for the finished product		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Minor change to an approved analytical procedure	1, 2, 3,	1, 2	IA
b)	Deletion of an analytical procedure if an alternative procedure is already authorised	4	1	IA
c)	Introduction, replacement, or substantial change to a biological/immunological/immunochemical analytical procedure for a finished product .			II
d)	Other changes to an analytical procedure for a finished product (including replacement or addition)		1, 2	IB
e)	Update of the analytical procedure to comply with the updated general monograph in the Ph. Eur.	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 analytical procedure is at least equivalent to the former 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 analytical procedure is not a biological/immunological/immunochemical procedure.			
5.	The registered analytical 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 analytical procedure and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new analytical procedure unless the new analytical procedure is added as an alternative procedure to a current one.			

911 **B.II.d.3**

B.II.d.3 Variations related to real-time release testing in the manufacture of the finished product	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
			II

912 ***B.II.e) Container closure system***

913 **B.II.e.1**

B.II.e.1 Change in immediate packaging of the finished product		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	**Change in qualitative and quantitative composition**			

	1. Solid pharmaceutical forms	1, 2, 3, 5	1, 2, 3, 4, 6	IA
	2. Semi-solid and non-sterile liquid pharmaceutical forms		1, 2, 3, 5, 6	IB
	3. Sterile medicinal products			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,	IB
	2. Sterile 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, 7	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 competent authorities 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.			
5.	The finished product is not a biological medicinal product.			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), including revised product information as appropriate.			
2.	Appropriate data on the new packaging (comparative data on permeability e.g. for O2, CO2 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 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 3 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 shelf life (with proposed action).			
6.	Comparative table of the current and proposed immediate packaging specifications, if applicable.			
7.	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.				

914 **B.II.e.2**

B.II.e.2 Change in shape or dimensions of the container or closure (immediate packaging)		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Non-sterile medicinal products	1, 2, 3	1, 3,	IA
b)	Sterile medicinal products		1, 2, 3	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 or industrial scale batches 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 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).			
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.	Re-validation studies have been performed in case of sterile products. The batch numbers of the batches used in the re-validation studies should be indicated, where applicable.			
3.	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 (at least three months stability data for least two pilot scale or industrial scale batches) 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 competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).			

915 **B.II.e.3**

B.II.e.3 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)		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Change that affects the product information	1	1	IA_{IN}
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.			

916 **B.II.e.4**

	B.II.e.4 Change in the specification attribute and/or acceptance criteria of the immediate packaging of the finished product	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Change within the specification acceptance criteria	1, 2, 3, 4	1, 2	IA
b)	Addition of a specification attribute to the specification with its corresponding analytical procedure	1, 2, 5	1, 2, 3, 5,	IA
c)	Deletion of a non-significant or obsolete specification attribute	1, 2	1, 2, 4	IA
d)	Replacement of a specification attribute with its corresponding analytical procedure		1, 2, 3	IB
Conditions				
1.	The change is not a consequence of any commitment from previous documentation checks to review specification acceptance criteria (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 and is not as a result of a safety or quality issue.			
3.	Any change should be within the range of currently approved acceptance criteria.			
4.	The analytical procedure remains the same, or changes in the procedure are minor.			
5.	Any new analytical procedure 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 procedure and validation data, where relevant.			
4.	Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.			
5.	Justification of the new specification attribute and the acceptance criteria.			
(*)	Note: This variation category is not intended to include changes in relation to revisions of the control strategy with an intention to minimise redundant testing of parameters and attributes (critical or non-critical) that are tested at different stages during the production, or cases where process/ product characterisation performed after authorisation has shown that the attribute/ parameter is non-critical. Such changes require regulatory assessment and are to be handled as Type IB or II variations as appropriate.			

917 **B.II.e.5**

	B.II.e. 5 Change in analytical procedure for the immediate packaging of the finished product	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Minor changes to an approved analytical procedure	1, 2, 3	1, 2	IA
b)	Other changes to a analytical procedure (including replacement or addition)	1, 3	1, 2	IA
c)	Deletion of a analytical procedure if an alternative analytical procedure is already authorised	4	1	IA
Conditions				
1.	Appropriate validation studies have been performed in accordance with the relevant guidelines and validation studies show that the updated analytical procedure is at least equivalent to the former analytical 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 analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
4.	An alternative analytical procedure is already authorised for the specification attribute 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 analytical procedure and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new analytical procedure.

918 **B.II.e.6**

B.II.e. 6 Change in pack size of the finished product		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. 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	IA_{IN}
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			II
d)	Change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) products		1, 2, 3	IB
e)	Addition of or change to a calendar package for a pack size already registered in the dossier.	2	1	IA_{IN}
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.				

919 **B.II.e.7**

B.II.e.7 Change in manufacturer, sterilisation process or supplier of packaging components (when mentioned in the dossier)		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Addition or replacement of a manufacturer or supplier	1, 2, 3, 4	1, 2	IA
b)	Addition or replacement of a site responsible for sterilisation of a packaging component, or a change to the sterilisation process		3, 4	IB

Conditions			
1.	No deletion of packaging component		
2.	The qualitative and quantitative composition of the packaging components and design specifications remain the same.		
3.	The specifications and quality control analytical procedure 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.	Comparative table of current and proposed specifications, if applicable.		
3.	Description of the sterilisation method and sterilisation cycle. Validation of the sterilisation cycle if the sterilisation cycle does not use the reference conditions stated in the Ph.Eur.		
4.	Evidence that the sterilisation has been conducted and validated in accordance with GMP and/or releavant ISO standards, as per guideline on the *sterilisation of the medicinal product, active substance, excipient and primary container*.		

920 **B.II.e.8**

B.II.e.8 Change of a secondary packaging component of the finished product (including replacement or addition), when mentioned in the dossier		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
		1, 2, 3, 4	1	IA
Conditions				
1.	The secondary packaging does not play a functional role on the stability of the finished product, or if it does, it is not less protective than the approved one.			
2.	The changed packaging component must be adequate for the storage of the finished product at the authorised conditions.			
3.	The change should not be due to critical deficiencies of the former packaging component.			
4.	The change is not a result of any unexpected events arising during manufacture or storage of the finished product.			
Documentation				
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

921 ***B.II.f) Stability***

922 **B.II.f.1**

B.II.f.1 Change in the shelf-life or storage conditions of the finished product		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Reduction of the shelf life of the finished product			
1.	As packaged for sale	1, 6	1, 2, 3	IA_{IN}
2.	After first opening	1, 6	1, 2, 3	IA_{IN}
3.	After dilution or reconstitution	1, 6	1, 2, 3	IA_{IN}
b)	Extension of the shelf life of the finished product			
1.	As packaged for sale (supported by real time data, fully in line with the stability protocol)	3, 4, 5	1, 2, 3	IA_{IN}
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 of the finished product based on extrapolation not in accordance with relevant stability guidelines or based on stability modelling			II
	5. Extension of the shelf-life of the finished product based on extrapolation of stability data in accordance with relevant stability guidelines		1, 2, 3	IB
c)	Change in storage conditions of a biological finished product			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 of the finished product	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.			
3.	Stability studies have been performed in accordance with a currently approved stability protocol. Real time data are submitted. All batches meet their pre-defined specification at all time points. No trends have been observed.			
4.	Product is not a biological or herbal medicinal product.			
5.	Product is an immediate release film-coated tablet.			
6.	Product is not on the Union list of Critical Medicines or similar national list (where applicable).			
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 [3 batches (unless otherwise justified) for biological medicinal products] 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.			
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).			
([1]) Pilot scale batches can be accepted with a commitment to verify the shelf life on production scale batches.				

923 ***B.II.g) Additional regulatory tools***

924 **B.II.g.1**

B.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	New design space for one or more unit operations in the manufacturing process of the finished product including the resulting in-process controls and/or analytical procedures		1, 2, 3	II
b)	New design space (method operable design range (MODR)) for a analytical procedures for excipients / intermediates and/or the finished product.		1, 2, 3	II
c)	Extension of an approved design space for the finished product and/or analytical procedures for excipients / intermediates and/or the finished product		1, 2, 3	IB
Documentation				
1.	The design space has been developed in accordance with the relevant European and international scientific guidelines. Results from product and process development studies (including risk assessment and multivariate studies, as appropriate) demonstrating that a systematic 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, and/or in the form of mathematical equation, as relevant, including the variables (material attributes and process parameters, as appropriate) with their proposed ranges and limits.
3.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).

925 **B.II.g.2**

B.II.g.2 Introduction of a post approval change management protocol related to the finished product	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. 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).			

926 **B.II.g.3**

B.II.g.3 Deletion of an approved change management protocol related to the finished product	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
	1	1, 2	IA
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).			

927 **B.II.g.4**

B.II.g.4 Changes to an approved change management protocol	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. 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 the changes do not change the overall strategy defined in the protocol and are not broader than the currently approved protocol.			

928 **B.II.g.5**

B.II.g.5 Implementation of changes foreseen in an approved change management protocol	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a) The Implementation of changes foreseen in a PACMP via Type IA notification	1	1, 2, 3, 4	IA
b) The Implementation of changes foreseen in a PACMP via Type IA_{IN} notification	2	1, 2, 3 4	IA_{IN}

c)	Implementation of change foreseen in a PACMP via Type IB notification		1, 2, 3, 4	IB
Conditions				
1.	The proposed change has been performed fully in line with the approved change management protocol, which requires its notification within 12 months following implementation.			
2.	The proposed change has been performed fully in line with the approved change management protocol, which requires its immediate notification following implementation.			
Documentation				
1.	Reference to the approved change management protocol.			
2.	Declaration that the change is in accordance with the approved change management protocol and that the study results meet the acceptance criteria specified in the protocol.*			
3.	Results of the studies performed and any other supporting documentation in accordance with the approved change management protocol.			
4.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
	Note: *In case the acceptance criteria and / or other conditions in the protocol are not met, the change cannot be implemented as a variation of this category and should instead be submitted as variation of the applicable category without PACMP.			

929 **B.II.g.6**

B.II.g.6 Introduction of a product lifecycle management document related to the finshed product	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
		1, 2, 3	II
Documentation			
1. The content of the product lifecycle management document has been developed in accordance with the relevant European and international scientific guidelines. Results from product, process and analytical development studies (including risk assessment and multivariate studies, as appropriate) demonstrating that a systematic understanding of how material attributes and process parameters impact the critical quality attributes of the finished product has been achieved.			
2. The product lifecycle management document includes a description of the material attributes, quality attributes and process parameters (or analytical procedure parameters), their proposed limits and ranges, and future variation reporting categories, in a tabular format.			
3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

930 **B.II.g.7**

B.II.g.7 Changes to process parameters or quality attributes related to the finished product as described in a product lifecycle management document		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Major change to a process parameter or quality attribute		1, 2, 3	II
b)	Minor change to a process parameter or quality attribute	1	1, 2, 3	IA
c)	Minor change to a process parameter or quality attribute	2	1, 2, 3	IA_{IN}
d)	Other changes to a process parameter or quality attribute		1, 2, 3	IB
Conditions				
1.	The change has been foreseen in the product lifecycle management document as a Type IA variation requiring notification within 12 months following implementation			
2.	The change has been foreseen in the product lifecycle management document as a Type IA variation requiring immediate notification following implementation			
Documentation				

1.	A summary and justification of the proposed change(s), clearly describing the present and proposed situation and supporting documentation.
2.	An updated product lifecycle management document including updated description of the material attributes, quality attributes or process parameters (or analytical procedure parameters), as appropriate, their proposed limits and ranges, and future variation reporting categories, in tabular format.
3.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).

931 ***B.II.h) Adventitious Agents Safety***

932 **B.II.h.1**

B.II.h.1 Update to the "Adventitious Agents Safety Evaluation" information (section 3.2.A.2)		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. 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).			

933 ***B.III CEP/TSE/MONOGRAPHS***

934 **B.III.1**

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**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	**European Pharmacopoeial certificate of suitability to the relevant Ph. Eur. Monograph.**			
1.	New certificate of suitability (CEP)	1, 2, 3, 4, 5, 8	1, 2, 3, 4,	IA_{IN}
2.	Update of an approved certificate of suitability (CEP)	1, 2, 3, 4, 8	1, 2, 3, 4,	IA
3.	Deletion of certificate(s) of suitability (CEP)	7	2	IA
4.	New certificate of suitability (CEP) 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	IB
5.	New or updated certificate of suitability (CEP) for a herbal active substance		1, 2, 4, 6	IB
b)	**European Pharmacopoeial TSE certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient**			

1.	New TSE certificate for an active substance from a new or an already approved manufacturer	3, 6	1, 2, 3, 4,	IA_{IN}
2.	New TSE certificate for a starting material/reagent/ intermediate/or excipient from a new or an already approved manufacturer	3, 6	1, 2, 3, 4,	IA
3.	Updated TSE certificate from an already approved manufacturer	3, 6	1, 2, 3, 4,	IA
4.	Deletion of TSE certificate(s)	7	2	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 impact of the new source of the active substance, or changes to the active substance, on the finished product has been fully evaluated and there is no change in Critical Quality Attributes or composition of the finished product (e.g. API mix). The finished product release and end of shelf life specifications remain the same.
2.	Unchanged MAH/FPM active substance specification for impurities. This applies to organic impurities, residual solvents, mutagenic impurities (including nitrosamines) and elemental impurities. Tightening of impurity limits, changes to specifications for impurities according to the Ph. Eur. and/or residual solvents according to ICH Q3C, are excluded. and Where applicable, unchanged MAH/FPM active substance specification for polymorphism, hydration state, particle size profile, or any other specific requirements that may impact FP quality.
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, or if it does, the update of the CEP/TSE Certificate is only due to administrative changes.
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.	If Gelatin 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.
7.	At least one manufacturer for the same substance remains in the dossier.
8.	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 comply with the guideline on water for pharmaceutical use regarding bacterial endotoxins and microbiological quality.
Documentation	
1.	Copy of the current (updated) Ph. Eur. certificate of suitability (CEP) and the letter of access (where available).
2.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format). This should include: • Updated consolidated list of manufacturers of the active substance (section 3.2.S.2.1). • Updated single compiled MAH/FPM active substance specification, including analytical methods and method validation (where the FPM uses analytical procedures which are different from the Ph. Eur. monograph or from those used by the CEP holder), and batch results from testing carried out by the MAH/FPM (Section 3.2.S.4.1-3.2.S.4.4).
3.	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).
4.	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.
5.	Suitable evidence to confirm compliance of either the water used in the final steps of the synthesis of the active substance, or the active substance, itself with the corresponding requirements of the guideline on quality of water for pharmaceutical use regarding bacterial endotoxins and microbiological quality.
6.	For herbal active substances a detailed comparison regarding specifications and critical quality attributes (e.g. for extracts: reference to the herbal starting material (incl. scientific binominal name and plant part), physical state, extraction solvent (nature and concentration), drug extract ratio (DER) and manufacturing process (including a stepwise comparison of all manufacturing steps in tabular format).
	Note: For active substances supported by a certificate of suitability (CEP), a separate variation is required under category B.I.a.1 scope in the following scenarios; -to register or amend sites (e.g. micronisation or control/testing sites) if these sites are not included on the CEP. -to register or amend in-house analytical test procedures used by FPM if these analytical procedures are not included on the CEP. -to register or amend a re-test period if the re-test period is not included on the CEP.

935 **B.III.2**

B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State for active substances, intermediates, excipients, immediate packaging materials and active substance starting materials		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. 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	1, 2, 3, 4	IA_{IN}
	2. Excipient/active substance starting material/intermediate/immediate packaging material	1, 2, 3, 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	1, 2, 3, 4	IA
c)	Change in specifications from a national pharmacopoeia of a Member State to the Ph. Eur.	1, 4	1, 2, 3, 4	IA
d)	Change related to a herbal active substance or herbal starting material		1, 2, 3, 4, 5	IB
Conditions				
1.	The change is made exclusively to fully comply with the pharmacopoeia. All the analytical procedures in the specification need to correspond to the pharmacopoeial standard after the change, except any additional supplementary procedures.			
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.	Suitability of the new or changed pharmacopoeial analytical procedure has been confirmed under the actual condition of use.			
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 analytical procedures 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.
5.	For herbal active substances/herbal starting materials a detailed comparison regarding their characteristics (e.g. for extracts: reference to the herbal starting material (incl. scientific binominal name and and plant part, physical state extraction solvent (nature and concentration), drug extract ratio (DER) and the manufacturing process) should be provided.
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.	

936 ## *B. IV MEDICAL DEVICES*

937 **B.IV.1**

B.IV.1	**Changes to device (parts) co-packaged with the medicinal product or referenced in the product information**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Addition or replacement of a co-packaged device part) or referenced device	1, 2, 3, 5	1, 2, 3	IA_{IN}
b)	Addition, replacement or other changes of a co-packaged or referenced device that may have a significant impact to the delivery, quality, safety and/or efficacy of the medicinal product			II
c)	Deletion of a co-packaged or referenced device	3, 4, 5	1, 4	IA_{IN}
d)	Minor change for a co-packaged device (part) or referenced device that does not impact the performance and safety of the device, nor that affects the quality of the product or the usability of the device	1, 3, 5	1	IA
Conditions				
1.	The device does not have a significant impact on the delivery or use of the medicinal product			
2.	Compatibility studies have been finalised and the 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 safely and accurately delivered.			
5.	There is no impact to the Risk Management Plan.			
Documentation				
1.	Amendment of the relevant section(s) of the dossier , including description, detailed drawing and composition of the device material, compatibility and usability studies as appropriate.			
2.	For the addition or replacement of a co-packaged medical device, evidence that relevant standards have been met e.g. EU Declaration of Conformity or, where applicable, EU certificate, or other appropriate documentation such as summary information confirming compliance with relevant General Safety and Performance Requirements.			
3.	Data to demonstrate performance, safety and compatibility of the device, as appropriate.			
4.	Justification for the deletion of the device.			

938 **B.IV.2**

B.IV.2	Changes to an integral medical device (part)	Cond. To be fulfilled	Docum. To be supplied	Proced. Type
a)	Addition or replacement of an integral device (part) or major change to the materials and/or design and/or performance characteristics of an integral device which may have a significant impact on the delivery or the quality, safety, or efficacy of the medicinal product.			II
b)	Addition or replacement of an integral device (part) which does not have a significant impact on the performance, delivery, quality, safety or efficacy of the medicinal product		1, 2	IB
c)	Deletion of an integral medical device (part) that does not lead to the complete deletion of a strength or pharmaceutical form	1, 2	1	IA_{IN}
d)	Change of a material of a device (part) not in contact with the medicinal product	3, 4	1	IA
e)	Change of a material of a device (part) in contact with the medicinal product that does not have a significant impact on the safety, quality or efficacy of the medicinal product or does not contain materials of human or animal origin for which assessment is required of viral safety data or TSE risk.		1, 3, 4	IB
f)	Addition or replacement of a supplier/manufacturer of an existing device (part)	5, 6	1	IA
g)	Addition or replacement of a site responsible for sterilization of the device (part) or change to the sterilisation process of the device (part) when supplied as sterile		1, 5, 6	IB
h)	Other minor change to an integral device (part)	3, 4	1	IA
Conditions				
1.	The medicinal product can still be safely and accurately delivered.			
2.	The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.			
3.	The change has no impact on the performance, delivery, safety or quality of the finished product. The functionality must remain the same.			
4.	There is no substantial amendment of the product information			
5.	There is no change to the device (part)			
6.	The supplier/manufacturer does not perform sterilisation			
Documentation				
1.	Amendment of the relevant section(s) of the dossier , including revised product information as appropriate.			
2.	EU Declaration of Conformity (Class I devices only), Notified Body Opinion confirming full compliance with the relevant General Safety and Performance Requirements or EU Certificate, as appropriate.			
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 competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action)			
4.	Where appropriate, proof must be provided that no interaction between the medicinal product and the device (part) occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the device), including confirmation that the material complies with relevant pharmacopoeial requirements or legislation of the Union on plastic material and objects in contact with foodstuffs. Comparative data on permeability e.g. for O2, CO2 moisture should be provided as appropriate.			

5.	Evidence that the sterilisation has been conducted and validated in accordance with GMP and/or relevant ISO standards, as per guideline on the sterilisation of the medicinal product, active substance, excipient and primary container.
6.	Description of the sterilisation method and sterilisation cycle. Validation of the sterilisation cycle if it does not use the reference conditions stated in Ph. Eur.

939 **B.IV.3**

B.IV.3	**Changes to the dimensions, specification parameters and/or specification limits or analytical procedures for an integral medical device (part)**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Minor change to the dimensions of a medical device (part)	1, 2, 3, 4	1	IA
b)	Change to the specification for a medical device (part) that is not part of the final product specifications			
	1. Change within the specifications acceptance criteria of the currently approved specifications, including amendments to more accurately describe the appearance	1, 2, 4, 5	1,	IA
	2. Addition of a new specification attribute with its corresponding analytical procedure	1, 2, 8	1, 2, 3	IA
	3. Replacement of a specification attribute with its corresponding analytical procedure		1, 2, 3	IB
	4. Widening of a specification acceptance criteria or deletion of a specification attribute that has a significant impact on the quality, safety, performance or usability of the device			II
c)	Change to an analytical procedure for the medical device (part)			
	1. Addition, replacement or other change to an approved analytical procedure	1, 6	1, 2, 4	IA
	2. Deletion of a test procedure if an alternative an analytical procedure is already authorised	1, 7	1	IA

	Conditions
1.	The change does not impact the delivery, use, safety or stability of the finished product.
2.	No change in the qualitative or quantitative composition of the device (part)
3.	No change in the headspace or in the surface/volume ratio, or minor changes that do not impact the stability of the final product
4.	The change should be in the range of currently approved specification acceptance criteria
5.	The analytical procedure remains the same or changes to the analytical procedure are minor
6.	Appropriate validation studies have been performed in accordance with the relevant guidelines and validation studies show that the updated analytical procedure is at least equivalent to the former analytical procedure (when appropriate).
7.	An alternative analytical procedure is already authorised for the specification attribute .
8.	The change is not the result of a safety or quality issue
	Documentation
1.	Amendment of the relevant section(s) of the dossier
2.	Details of any new analytical procedure and validation, where relevant
3.	Justification of the specification attribute and its acceptance criteria
4.	Comparative validation results or if justified comparative analysis results showing that the current analytical procedure and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new analytical procedure.

Note: classification applicable to specifications and analytical procedures for the medical device (part) only. Analytical procedures and specifications that are part of the final product specification and control strategy should be classified under the appropriate B.II category.

B.V. CHANGES TO A MARKETING AUTHORISATION RESULTING FROM OTHER REGULATORY PROCEDURES

B.V.a) PMF/VAMF

B.V.a.1

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)	Cond. to be fulfilled	Docum. to be supplied	Proced. 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, 6	IB
c)	Inclusion of an updated/amended Plasma Master File when changes affect the properties of the finished product		1, 2, 3, 4, 5, 6	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, 6	IA
Conditions				
1.	The updated or amended Plasma Master File has been granted a certificate of compliance with legislation of the Union in accordance with 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.			
5.	Updated affected sections of the dossier for the medicinal product.			
6.	Updated product information whenever this is required by the relevant national legislation.			

B.V.a.2

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)	Cond. to be fulfilled	Docum. to be supplied	Proced. 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 Vaccine Antigen Master File has been granted a certificate of compliance with legislation of the Union in accordance with Annex I to Directive 2001/83/EC.			
Documentation				
1.	Declaration that the 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.

945 **B.V.b) Referral**

946 **B.V.b.1**

B.V.b.1	**Update of the quality dossier intended to implement the outcome of a Union referral procedure**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. 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.			

947 # C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES

948 General Note: In case of a change in therapeutic indication, posology or maximum daily dose, a review
949 of quality documentation should be performed. A justification should be provided, considering the
950 impact of the changes on quality documentation (for example, the need to change impurity limits or
951 warnings for excipients with known effect/ threshold).

952 **C.1.**

C.1	**Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. 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			**II**
Conditions				
1.	The variation implements the wording exactly as 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.

953 **C.2.**

C.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 from the original application		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Implementation of change(s) for which no new additional data is required to be submitted by the MAH		**1, 2, 3**	**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.			
3.	For the biosimilar medicinal product aligning the product information with an indication of the reference medicinal product: a justification that the comparability exercise performed for the biosimilar medicinal product is valid for the applied indication.			

954 **C.3**

C.3 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Article 45 or 46 of Regulation (EC) No 1901/2006, or the outcome of a PRAC signal recommendation, or to adapt to a joint recommendation of EU competent authorities (e.g., a Core SmPC, or following the assessment of an Urgent Safety Restriction etc.)		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Implementation of the agreed wording	**1**	**1, 2**	**IA IN**
b)	Implementation of the agreed wording that requires additional minor assessment, e.g., translations are not yet agreed upon.		**1, 2**	**IB**
c	Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH			II
Conditions				
1.	The variation implements the wording exactly as requested, including agreed national translations, 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 authoritiesies.			
2.	Revised product information.			

955 **C.4**

C.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data.	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**

			II

956 **C.5**

C.5 Change in the legal status of a medicinal product for centrally authorised products	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a) For generic/hybrid/biosimilar medicinal products following an approved legal status change of the reference medicinal product		1,2	IB
b) All other legal status changes			II
Documentation			
1. Attached to the cover letter of the variation application: proof of authorisation of the legal status change (e.g. reference to the Commission Decision concerned).			
2. Revised product information.			
Note: for Nationally Authorised Products approved via MRP/DCP, the change of the legal status is to be handled at national level (not via a MRP variation).			

957 **C.6**

C.6 Change(s) to therapeutic indication(s)	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a) Addition of a new therapeutic indication or modification of an approved one			II
b) Deletion of a therapeutic indication		1	IB
Documentation			
1. Amendment of the relevant section(s) of the dossier, including revised product information			
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.1 and C. 2 apply, respectively.			

958 **C.7**

C.7 Deletion of:	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a) a pharmaceutical form		1,2	IB
b) a strength		1,2	IB
Documentation			
1. Declaration that the remaining product presentation(s) are adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.			
2. Revised product information			
Note: in cases where a given pharmaceutical form or strength has received a marketing authorisation which is separate to the marketing authorisation for other pharmaceutical forms or strengths, the deletion of the former will not be a variation but the withdrawal of the marketing authorisation.			

959 **C.**8

C..8 Introduction of a summary of pharmacovigilance system for medicinal products for human use	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**

a)	Introduction of a summary of pharmacovigilance system after a change of the MAH		1,2	**IA IN**
Documentation				
1.	Summary of the pharmacovigilance system: — Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance and a statement 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.			
2.	PSMF number (if available)			
Note: This variation is only applicable for nationally authorized products in order to prove for the new MAH that he has at his disposal a qualified person responsible for pharmacovigilance and a statement signed by the new MAH 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. For centrally authorized products this is not needed as the change is covered by the MA transfer procedure.				

960 **C.9**

C.9 Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Implementation of minor changes to reflect the outcome of previous assessment	**1**	**1, 2**	**IA IN**
b)	Implementation of changes which require additional minor assessment, e.g. change to the due date of obligations and conditions of a marketing authorisation and required pharmacovigilance activities in the risk management plan, including changes to the due date of study milestones, and template updates.		2	**IB**
c)	Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the competent authority is required			**II**
Conditions				
1.	The variation implements the action requested, including the exact agreed wording and the agreed national translations, 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 competent authorities.			
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.				

961 **C.10**

C.10 Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring		**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. 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).	

962 **C.11**

C.11 Submission of results of assessments carried out on target patient groups in order to comply with Article 59(3) of Directive 2001/83/EC and any resulting change(s) to the Package Leaflet.	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
		1,2	IB
Documentation			
1. Results of consultation with target patient groups (user test or bridging report).			
2. Revised product information			

963 **C.12**

C.12 Other variations not specifically covered elsewhere in this Annex which involve the submission of studies, including bioequivalence studies, to the competent authority	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
			II
Note: This variation scope includes the submission of studies where no changes to the Summary of Product Characteristics, Labelling or Package Leaflet are initially proposed by the MAH. 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 (EC) No 1901/2006 is likewise covered by this variation (provided that the requirements under Regulation (EC) No 1901/2006 have been met).			

964

965 # D. PMF / VAMF

966 **D.1**

D.1	**Change in the name and/or address of the certificate holder**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	PMF certificate holder	1	1	IA_{IN}
b)	VAMF certificate holder	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.			

967 **D.2**

D.2	**Change or transfer of the current PMF certificate holder to a new PMF certificate holder, i.e. different legal entity**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. 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.

968 **D.3**

D.3	**Change in the name and/or address of a blood establishment and / or blood/plasma collection centres**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. 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).			
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.			

969 **D.4**

D.4	**Addition or relocation of a blood/plasma collection centre within a blood establishment already included in the PMF**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
a)	Relocation	1, 2, 3	2, 3	IA
b)	Addition		1, 2, 3	IB
Conditions				
1.	It remains the same legal entity.			
2.	Inspection authorities have issued new inspection approval status			
3.	The blood/plasma collection centre should retain the same staff, equipment and quality system.			
Documentation				
1.	Epidemiological data for viral markers related to the blood/plasma collection centre to be provided as requested in the 'Guideline on epidemiological data on blood transmissible infections.'			
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 including also inspections and audit information.			

970 **D.5**

D.5	**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**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**

	1. Deletion	1	1	IA
	2. Change of status			
	a) operational to non-operational	1	1	IA
	b) from non-operational to operational	2, 3, 4	1, 2, 3, 6	IA
	c) from non-operational to operational when epidemiological data has not been annually submitted or there have been changes in blood establishment or centres since there were moved to non-operational (e.g. blood bags, testing kits)		1, 4, 5, 6	IB
Conditions				
1.	The deletion or change of status should not relate to a GMP issue or other safety reasons.			
2.	The establishments(s)/centre(s) should comply with the legislation in terms of inspections.			
3.	There have been no changes in blood establishment or centres since there were moved to non-operational (e.g. blood bags, testing kits) and standard contract between blood establishment and PMF holder is in place.			
4.	For collection centres epidemiological data have been annually submitted and evaluated in the PMF Annual Update.			
Documentation				
1.	Updated relevant sections and annexes of the PMF dossier including inspections and audit information, as needed.			
2.	Declaration no changes have been implemented			
3.	Declaration that, while the establishment(s)/centre(s) has remained in non-operational, the Epidemiology data have been submitted annually			
4.	Updated epidemiological data for viral markers related to the blood/plasma collection centre			
5.	Declaration of changes introduced, and variation applications submitted.			
6.	Confirmation that standard contract between blood establishment/centre and PMF holder is in place.			

971 **D.6**

D.6	**Addition of a new blood establishment for the collection of blood/plasma not included in the PMF**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
				II

972 **D.7**

D.7	**Addition or relocation of a centre/laboratory for testing of donations and/or plasma pools within an establishment already included in the PMF**	**Cond. to be fulfilled**	**Docum. to be supplied**	**Proced. type**
	a) Relocation	1, 2, 3	1, 2	IA
	b) Addition		1, 2	IB
	c) Link existing collection centres to another existing or new Blood/plasma testing centres in PMF		2	IA
Conditions				
1.	It remains the same legal entity.			
2.	Inspection authorities have issued new inspection approval status.			
3.	The centre/laboratory should retain the same staff, equipment and quality system.			
Documentation				
1.	Statement that the testing is performed following the same SOPs and/or analytical procedures as already accepted.			
2.	Updated relevant sections and annexes of the PMF dossier including inspections and audit information.			

973 **D.8**

D.8	Addition of a new laboratory for testing of donations and/or plasma pool not included in the PMF	Cond. to be fulfilled	Docum. to be supplied	Proced. type
				II

974 **D.9**

D.9	Changes of an establishment or centre(s) in which storage of plasma is carried out or organization(s) involved in the transport of plasma	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	a) Relocation of storage establishment or centre	1, 2	1, 2	IA
	b) Addition		2	IB
	c) Deletion	3	2	IA
Conditions				
1.	It remains the same legal entity.			
2.	Inspection authorities have issued new inspection approval status.			
3.	The reason for deletion should not be related to a GMP issues.			
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 including inspections and audit information, as needed.			

975 **D.10**

D.10	Addition or replacement of blood and plasma tests	Cond. to be fulfilled	Docum. to be supplied	Proced. type
a)	Test kit for individual donations			
	1. CE marked	1	1, 2	IA
	2. Non CE-marked, not previously been approved in the PMF for any blood centre for testing of donations			II
	3. Non-CE-marked, previously approved in the PMF for other blood centre(s) for testing of donations		1, 2	IB
b)	Test for mini-pools NAT			
	1. CE-marked	1	1, 2	IA
	2. non CE-marked		1,2	IB
c)	Test for Plasma pools (antibody, antigen or NAT test).			II
Conditions				
1.	The new test kit is CE-marked and used in line with instructions of use.			
Documentation				
1.	List of testing site(s) where the test 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".			

976

977 **D.11**

D.11 Change of inventory hold procedure	Cond. to be fulfilled	Docum. to be supplied	Proced. type
		1	IA
Documentation			
1. Updated relevant sections of the PMF dossier.			

978 **D.12**

D.12	Addition or replacement of blood containers (e.g. bags, bottles)	Cond. to be fulfilled	Docum. to be supplied	Proced. type
a)	The new blood containers are CE-marked	1	1	IA
b)	The new blood containers are not CE-marked and there is no impact on the quality criteria of the blood in the container		1, 2, 3	IB
c)	The new blood containers are not CE-marked and there is potentially an impact on the quality criteria of the blood in the container			II
Conditions				
1.	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.			
2.	Confirmation and data demonstrating compliance with equivalent quality standard as CE-mark as requested in the ‘Guideline on the scientific data requirements for a PMF.			
3.	Confirmation that any anticoagulant solution complies with PhEur requirements.			
4.	Justification that there is no impact on the quality criteria of the blood in the container.			

979 **D.13**

D.13	Change in storage / transport	Cond. to be fulfilled	Docum. to be supplied	Proced. 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).			

980 **D.14**

D.14	Introduction of test for a new viral marker when this will have significant impact on the viral risk assessment	Cond. to be fulfilled	Docum. to be supplied	Proced. type

			II

981 **D.15**

D.15	Change in the plasma pool preparation (e.g. manufacturing method, pool size, storage of plasma pool samples)	Cond. to be fulfilled	Docum. to be supplied	Proced. type
			1	IB
Documentation				
1. Updated relevant sections of the PMF dossier.				

982 **D.16**

D.16	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)	Cond. to be fulfilled	Docum. to be supplied	Proced. type
				II

983