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COMMUNICATION FROM THE COMMISSION

Guidelines on the details of the various categories of variation, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 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

(C/2025/5045)

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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 variations to the terms of marketing authorisations.

Under Article 4 of the Variations Regulation the Commission is required to draw up guidelines on (i) the details of the various categories of variations, (ii) the operation of the procedures laid down in Chapters II, IIa, III and IV of the Variations Regulation and (iii) the documentation to be submitted pursuant to these procedures.

These guidelines apply to variations of marketing authorisations for medicinal products granted in accordance with Regulation (EC) No 726/2004 of the European Parliament and of the Council ([2]) and Directive 2001/83/EC of the European Parliament and of the Council ([3]). They are intended to facilitate the interpretation and application of the Variations Regulation. They provide details on the application of the relevant procedures, including the steps to be taken, from the submission of a notification or an application for a variation to the final outcome of the procedure.

The Annex to these guidelines provides details of the classification of variations into the categories defined in Article 2 of the Variations Regulation: minor variations of Type IA, minor variations of Type IB and major variations of Type II. It also provides further details, where appropriate, on the scientific data to be submitted for specific variations and how this data should be documented.

The Variation Regulation was amended in 2021, through Commission Delegated Regulation (EU) 2021/756 ([4]) and, also in 2024, the Variation Regulation was amended, through Commission Delegated Regulation (EU) 2024/1701 ([5]), in order to achieve efficiency gains and to reduce the administrative burden for the pharmaceutical industry and to better use the resources of the competent authorities through simplified and streamlined procedures, ensuring the same standards for quality, efficacy and safety of medicines.

These present guidelines replace the 2013 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 Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products, and on the documentation to be submitted pursuant to those procedures ([6]) (the '2013 guidelines').

The present guidelines reflect the 2024 amendment of the Variations Regulation and will apply from 15 January 2026. Submissions made prior to that date should follow the 2013 guidelines.

The present guidelines will be updated in accordance with Article 4 of the Variations Regulation, taking into account the Agency's recommendations on unforeseen variations, as referred to in Article 5, leading to new classifications of variations.

([1]) Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7, ELI: http://data.europa.eu/eli/reg/2008/1234/oj).

([2]) Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human use and establishing a European Medicines Agency (OJ L 136, 30.4.2004, p. 1, ELI: http://data.europa.eu/eli/reg/2004/726/oj).

([3]) Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use (OJ L 311, 28.11.2001, p. 67, ELI: http://data.europa.eu/eli/dir/2001/83/oj).

([4]) Commission Delegated Regulation (EU) 2021/756 of 24 March 2021 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 162, 10.5.2021, p. 1, ELI: http://data.europa.eu/eli/reg_del/2021/756/oj).

([5]) Commission Delegated Regulation (EU) 2024/1701 of 11 March 2024 amending Regulation (EC) No 1234/2008 as regards the examination of variations to the terms of marketing authorisations for medicinal products for human use (OJ L, 2024/1701, 17.6.2024, ELI: http://data.europa.eu/eli/reg_del/2024/1701/oj).

([6]) OJ C 223, 2.8.2013, p. 1.

The electronic version of the present guidelines, which may include new classifications of variations and the updates to the guidelines, will be published by the Commission on its website.

Definitions of terms used in these guidelines are provided in Directive 2001/83/EC, Regulation (EC) 726/2004 and in the Variations Regulation.

For the purpose of these guidelines:

'centralised procedure' means the procedure for granting marketing authorisations set out in Regulation (EC) No 726/2004;

'mutual recognition procedure' and 'decentralised procedure' mean the procedure for granting marketing authorisations set out in Chapter 4 of Directive 2001/83/EC;

'purely national procedure' means the procedure for granting marketing authorisations by a Member State in accordance with Directive 2001/83/EC outside the mutual recognition and decentralised procedure;

'centrally authorised medicinal products' means all marketing authorisations granted in accordance with the centralised procedure described above;

'nationally authorised medicinal products' means all marketing authorisations granted in accordance with the mutual recognition, decentralised and purely national procedures described above;

'variations for mutual recognition procedure' means the variation procedures conducted for applications concerning marketing authorisations granted in accordance with Chapter 4 of Directive 2001/83/EC as described above (via both the 'mutual recognition procedure' and the 'decentralised procedure');

'Member States concerned' means, in accordance with Article 2(6) of the Variations Regulation, a Member State whose competent authority has granted a marketing authorisation for the medicinal product in question;

'concerned Member States' means all Member States concerned except the reference Member State;

'national competent authority' means the competent authority of the Member State, in accordance with Article 2(9) of the Variations Regulation, that has granted a marketing authorisation under a purely national procedure;

'the Agency' means the European Medicines Agency;

'relevant authority' means the competent authority of each Member State concerned, or the Agency, in the case of centrally authorised medicinal products; and

'reference authority' means, in the context of the super-grouping and worksharing procedure, the Agency, where at least one of the marketing authorisations concerned is a centralised marketing authorisation, or the competent authority of the Member State chosen by the holder and accepted by that competent authority, or chosen by the coordination if none of the competent authorities of the Member States agrees to act as the reference authority, in the other cases.

2. PROCEDURAL GUIDANCE ON THE HANDLING OF VARIATIONS

Marketing authorisations lay down the terms under which the marketing of a medicinal product is authorised in the EU. They comprise:

— a decision granting the marketing authorisation (including the summary of the product characteristics and any conditions, obligations, or restrictions affecting the marketing authorisation, or changes to the labelling or the package leaflet related to changes to the summary of the product characteristics) issued by the relevant authority; and

— a technical dossier containing the data submitted by the holder in accordance with Articles 8(3) to 11 of Directive 2001/83/EC and Annex I thereto, Article 6 of Regulation (EC) No 726/2004 and Article 7 of Regulation (EC) No 1394/2007 of the European Parliament and of the Council ([7]).

The Variations Regulation governs the procedures for amending a decision granting the marketing authorisation and the technical dossier.

However, changes to the labelling or package leaflet that are not connected to the summary of product characteristics are not governed by the procedures of the Variations Regulation, in which case the procedure laid down in Article 61(3) of Directive 2001/83/EC should be followed instead.

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 of a variation application

An application for a variation shall be made electronically in the eCTD format ([8]), in accordance with the instructions laid down 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) ([9]) as follows:

— A cover letter.

— The completed EU electronic variation application form (eAF) (available at https://esubmission.ema.europa.eu), including (i) the details of the marketing authorisations concerned, (ii) a description of all individual variations submitted, (iii) the variation code as laid down in the Annex to these guidelines, its electronic version or a recommendation issued in accordance with Article 5 of the Variations Regulation and (iv), where applicable, confirmation that all documentation requirements have been met.

— A detailed present /proposed table must also be provided for all changes included in the submission. Where a variation is a consequence of, or related to, another variation, a description of the relationship 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 minor variation of Type IB (or major variation of Type II upon request from the holder when submitting the variation) must be included. Where a minor variation of Type IA is submitted, the date of implementation and confirmation that all conditions have been met should be provided.

([7]) Regulation (EC) No 1394/2007 of the European Parliament and of the Council of 13 November 2007 on advanced therapy medicinal products and amending Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 324, 10.12.2007, p. 121, ELI: http://data.europa.eu/eli/reg/2007/1394/oj).

([8]) https://esubmission.ema.europa.eu/ectd/index.html.

([9]) EudraLex – Volume 2 – Pharmaceutical legislation on notice to applicants and regulatory guidelines for medicinal products for human use (https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-2_en).

— The relevant documentation or data in support of the proposed variation, including, where applicable, any documentation specified in the Annex to these guidelines, should be provided. Where the variation affects the summary of product characteristics, labelling, package leaflet or the obligations and conditions of a centrally authorised medicinal product, the revised summary of product characteristics, labelling and package leaflet ('the product information') presented in the appropriate format should be included. For minor variations of Type IA or Type IB, translations of the product information should also be provided at the time of submission. In all other cases they should be provided immediately after a favourable opinion on the procedure for centrally authorised medicinal products, or, within seven (7) days of the end of the mutual recognition or decentralised procedure. Where the overall design and readability of the outer and immediate packaging or package leaflet is affected by the variation, the relevant authorities should be provided with mock-ups or specimens.

— In the case of (super-)grouping of variations concerning several marketing authorisations, or worksharing procedure, a common cover letter and eAF should be submitted along with supporting documentation for each variation applied for and, where applicable, revised product information for each medicinal product concerned. This will allow the relevant authorities to update the dossier of each marketing authorisation included in the (super-) grouping or worksharing procedure with the relevant amended or new information.

— In the case of variations requested by the competent authority resulting from new data submitted, e.g. in accordance with post-authorisation conditions or pharmacovigilance obligations, a copy of the request should be attached to the cover letter.

— In the case of a major variation of Type II or extension of marketing authorisation, an update or addendum to quality overall summaries, and non-clinical and clinical overviews should be provided, where relevant. Where non-clinical or clinical study reports are submitted, even if there is only one, a summary should be included in Module 2.

— In case of an extension to the marketing authorisation, supporting data relating to the proposed extension should be provided. Guidance on the appropriate additional studies required for such extensions can be found in Annex II to Chapter 1 of Volume 2A of the Notice to Applicants ([10]). Additionally, a full Module 1 should be provided, with justifications for the absence of data or documents included in the relevant section of Module 1.

Further details on the technical requirements regarding the submission of variations applications are provided on the websites of the Agency and the coordination group (CMDh) ([11]).

Any information relating to the implementation of a particular variation should be provided by the holder immediately upon request from the relevant authority.

Where a group of variations consists of different types of variation, the group must be submitted and handled according to the 'highest' variation type included in the group.

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

2.1. ***Minor variations of Type IA***

This section provides guidance 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.

([10]) https://health.ec.europa.eu/system/files/2019-07/vol2a_chap1_en_0.pdf.

([11]) The coordination group as referred to in Article 31 of Directive 2001/83/EC is also referred to as Co-ordination Group for Mutual Recognition and Decentralised procedures – Human (CMDh).

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

2.1.1. **Submission of minor variations of Type IA**

Minor variations of Type IA do not require prior examination by the competent authorities before they can be implemented by the holder. However, a notification of the minor variation of Type IA must be submitted simultaneously to all relevant authorities within 12 months of implementation.

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

2.1.1.1. *Grouping*

Pursuant to Articles 7(2) and 13d(2) of the Variations Regulation ('grouping'), the holder may submit several minor variations of Type IA for the same marketing authorisation under a single notification. For purely national procedures, such a notification may also cover one or several identical minor variations of Type IA for several marketing authorisations granted in the same Member State.

Without acceptance from the relevant authorities, a grouping of minor variations of Type IA not requiring immediate notification (for one marketing authorisation only), regardless of the route of the marketing authorisation procedure, may be used only within the context of an annual update, as described below (see Section 2.1.1.3).

2.1.1.2. *Super-grouping*

In addition to the above, under Article 7a of the Variations Regulation, a group of minor variations of Type IA may be submitted in a single notification 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 minor variations of Type IA listed in chapters E and Q of the Annex to these guidelines notified at the same time for several marketing authorisations granted in accordance with the mutual recognition, decentralised or purely national procedure in several Member States.

— One or several minor variations of Type IA notified at the same time for several marketing authorisations granted in accordance with the mutual recognition or decentralised procedure and the reference Member State is the same for those procedures.

— One or several minor variations of Type IA notified at the same time for several marketing authorisations granted in accordance with the centralised procedure.

— One or several variations of Type IA notified at the same time for several marketing authorisations granted in accordance with the mutual recognition, decentralised or purely national procedure in several Member States provided that the reference authority, in consultation with the concerned authorities, agrees to the proposed super-grouping.

As experience is acquired over time, additional cases may be identified in the future, in which case appropriate operational guidance will be provided on the Agency and CMDh websites accordingly.

2.1.1.3. *Annual update of minor variations of Type IA not requiring immediate notification*

Minor variations of Type IA not requiring immediate notification shall be collected and submitted as (i) an annual update, (ii) part of a grouping, together with variations of other types (as described in Section 2.2.1 and 2.3.1 of the guideline) or (iii) part of a super-grouping (as described above in Section 2.1.1.2). In the case of more than one minor variation of Type IA the annual update must meet the conditions for grouping or super-grouping, as specified above.

By way of an exception, individual submissions of one or several minor variations of Type IA may be accepted by the relevant authority, taking into account the cases listed on the Agency and CMDh websites.

2.1.2. **Minor variations of Type IA review under the mutual recognition and purely national procedures**

The reference Member State or the competent authority of a Member State, reviews the minor variation of Type IA within 30 days of receipt.

By day 30, the reference Member State or the competent authority of a Member State informs the holder and, where applicable, the concerned Member States, of the outcome of that review. Where the marketing authorisation requires any amendment to the decision granting said marketing authorisation, all Member States concerned shall amend the decision granting the marketing authorisation in accordance with the accepted variation within six (6) months of receiving 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 a single notification, the holder is informed which variations have been accepted or rejected following the review. The marketing authorisation holder must cease to implement any rejected variation.

2.1.3. **Minor variations of Type IA review under the centralised procedure**

The Agency reviews the minor variation of Type IA within 30 days of receipt, and the Agency provides the rapporteur with a copy of the minor variation of Type IA for information purposes only.

By day 30, the Agency informs 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 informs the Commission and sends the revised documentation. In such cases, the Commission amends the decision granting the marketing authorisation within 12 months.

Where one or several minor variations of Type IA are submitted as part of a single notification, the Agency clearly informs the holder which variations have been accepted or rejected following its review. The marketing authorisation holder must cease to implement any rejected variation.

2.2. ***Minor variations of Type IB***

This section provides guidance 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. After confirmation of a valid notification, and the notification of the start of the procedure, the holder must wait for 30 days before implementing the change to ensure that the notification is deemed acceptable by the relevant authorities.

2.2.1. **Submission of minor variations of Type IB**

Notifications of minor variations of Type IB must be submitted by the holder simultaneously to all relevant authorities.

2.2.1.1. *Grouping*

Holders may group under a single notification the submission of several minor variations of Type IB regarding the same marketing authorisation, or alternatively, group the submission of one or more minor variations 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 where this has been previously agreed with the reference Member State, the national competent authority or the Agency as appropriate.

In the case of 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 variations 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) that the competent authority has previously agreed to the grouping.

2.2.1.2. *Worksharing*

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 a single 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 a single application as 'worksharing', the holder shall amend their application.

2.2.2. **Variations of Type IB review under the mutual recognition and purely national procedures**

Notifications of a minor variation of Type IB notification shall be handled as follows:

Within seven (7) days, the reference Member State or the national competent authority, as applicable, checks whether the proposed change can be considered a minor variation of Type IB and whether the notification is valid ('validation') before the start of the procedure.

Where the proposed variation is not considered or classified as a minor variation of Type IB in accordance with the Annex to these guidelines (including any updated electronic version of these guidelines), or in a recommendation pursuant to Article 5 of the Variations Regulation, and the reference Member State or the national competent authority, as applicable, 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, where applicable, shall be informed immediately. In such cases, the holder is asked to amend their application and to complete it in accordance with the requirements for a major variation of Type II. Once the valid revised variation application has been received, a major variation of Type II assessment procedure is initiated (see Section 2.3.2).

Where the reference Member State or the national competent authority as applicable, is of the opinion that the proposed variation can be considered a minor variation of Type IB, the holder is informed of the outcome of the validation and notified of the start of the procedure.

Within 30 days of the acknowledgement of receipt of a valid notification and the notification of the start of the procedure, the competent authority notifies the holder of the outcome of the procedure. If the competent authority has not notified the holder of the outcome of the procedure within 30 days of the start of the procedure, the notification is deemed to have been accepted.

In the event of an unfavourable outcome, the holder may be asked to amend the notification within 30 days to take account of the grounds for that outcome. If the holder does not do so, the variation is deemed to have been rejected.

Within 30 days of receipt of the amended notification, the reference Member State or the national competent authority, as applicable, informs the holder of acceptance or rejection of the variation, including the grounds for the unfavourable outcome. Where applicable, the concerned Member States are informed of this.

Where a group of minor variations has been submitted as part of a single notification, the reference Member State or the national competent authority, as applicable, informs the holder and the concerned Member States as to which variations have been accepted or rejected. The holder may withdraw single variations from that group of variations during the procedure before the reference Member State or the national competent authority has finalised the review.

Where necessary, the relevant authorities will amend the marketing authorisation within six (6) months of the closure of the procedure. However, the accepted minor variations of Type IB may be implemented without waiting for the marketing authorisation to be amended.

2.2.3. **Minor variations of Type IB review under the centralised procedure**

The Agency handles notifications of a minor variation of Type IB as follows:

Within seven (7) days, the Agency checks whether the proposed change can be considered a minor variation of Type IB and whether the notification is valid ('validation') before the start of the procedure.

Where the proposed variation is not considered or classified as a minor variation of Type IB in accordance with the Annex to these guidelines (including any updated electronic version of these guidelines), or 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 is informed of the unfavourable outcome. In such cases, the holder is asked to amend their application and to complete it in accordance with the requirements for a major variation of Type II. Once the valid revised variation application has been received, a major variation of Type II assessment procedure is initiated (see Section 2.3.5).

Where the Agency is of the opinion that the proposed variation can be considered a minor variation of Type IB, the holder is informed of the outcome of the validation and notified of the start of the procedure.

The rapporteur is involved in assessing the notification of the minor variation of Type IB.

Within 30 days of the acknowledgement of receipt of a valid notification and the notification of the start of the procedure, the Agency notifies the holder of the outcome. If the Agency has not notified the holder of the outcome of the procedure within 30 days of the start of the procedure, the notification is deemed to have been accepted.

In the event of an unfavourable outcome, the holder may be asked to amend the notification within 30 days and to take due account of the grounds for the unfavourable outcome. If the holder does not amend the notification within 30 days as requested, the notification is rejected.

Within 30 days of receipt of the amended notification, the Agency informs the holder whether the variation has been accepted or rejected, including the grounds for an unfavourable outcome.

Where a group of minor variations is submitted as part of a single notification, the Agency informs the holder which variations have been accepted or rejected. The holder may withdraw single variations from the group of variations during the procedure before the Agency has finalised its assessment.

Where the opinion of the Agency is favourable and the variation affects the terms of the Commission decision granting the marketing authorisation, the Agency notifies the Commission and sends the relevant documentation. Where necessary, the Commission amends the marketing authorisation within 12 months. However, the accepted minor variation of Type IB may be implemented without waiting for the amendment of the Commission decision granting the marketing authorisation. The agreed variations are included in the annexes to any ongoing or subsequent regulatory procedure triggering the need to issue a Commission decision.

2.3. ***Major variations of Type II***

This section provides guidance 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 authorities before implementation.

2.3.1. **Submission of major variations of Type II**

Applications for major variations of Type II must be submitted by the holder simultaneously to all relevant authorities.

2.3.1.1. *Grouping*

Holders may group under a single application the submission of several major variations of Type II regarding the same marketing authorisation, or alternatively, group the submission of one or more major variations 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 where this has been agreed previously with the reference Member State, the national competent authority or the Agency, as appropriate.

In the case of 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 variations 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) that competent authority has previously agreed to the grouping.

2.3.1.2. *Worksharing*

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 a single 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 a single application as worksharing, the holder shall amend their application.

2.3.2. **Major variations of Type II assessment under the mutual recognition and purely national procedures**

Upon receiving a variation of Type II application, the application is handled as follows:

Before the start of the procedure the reference Member State or the national competent authority, as applicable, acknowledges receipt of a valid application of a major variation of Type II. The holder and the concerned Member States, where applicable, are informed of the timetable also before the start of the procedure.

In the case of the mutual recognition procedure, the reference Member State draws up a draft assessment report and a decision on the application in accordance with the timetable provided. These are then circulated to the holder, for information, and to concerned Member States, which send their comments to the reference Member State within the deadlines set out in the timetable.

During the procedure, the reference Member State or national competent authority, as applicable, may ask the holder to provide additional information, in which case the procedure is suspended until the information has been received.

2.3.3. **Outcome of variation of Type II assessment under the mutual recognition procedure**

After receiving the holder's response, the reference Member State finalises the draft assessment report and the decision on the application and circulates to the concerned Member States for comments and to the holder for information.

Within 30 days of receiving the assessment report and the decision, the concerned Member States acknowledge the decision and inform the reference Member State accordingly, unless a potential serious risk to public health is identified that prevents a concerned Member State from so doing. The Member State in question must inform the reference Member State within 30 days, and give detailed grounds for its position.

The reference Member State then refers the application to the coordination group for the application of Article 29(3), (4), and (5) of Directive 2001/83/EC to the points of disagreement and informs the holder and the concerned Member States accordingly. The holder is not entitled to initiate a referral.

Where an application concerning a grouping of variations that includes at least a major variation of Type II is referred to the coordination group, the decision on the variations not subject to the referral are suspended until the referral procedure has been completed. This also applies to referrals to the Committee for Medicinal Products for Human Use ('the Committee') under Articles 32 to 34 of Directive 2001/83/EC. However, only variations on which a potential serious risk to human health has been identified – i.e. not the whole group of variations – are discussed by the coordination group and where applicable by the Committee.

The reference Member State informs the holder and the concerned Member States of the acceptance or rejection of the variation, including the grounds for an unfavourable outcome.

Where several major variations of Type II, or a group of major variations of Type II with other minor variations have been submitted as a single application, the reference Member State informs the holders and the concerned Member States which variations have been accepted or rejected. The holder may withdraw single variations from the group of variations during the procedure before the reference Member State has finalised the procedure.

The accepted major variation of Type II may be implemented 30 days after the holder has been informed of the acceptance of the variation by the reference Member State, provided that the necessary documents to amend the marketing authorisation have been submitted to the Member State concerned. In cases where the application has been the object of a referral, the variation must not be implemented until the referral procedure has concluded that the variation has been accepted. However, the variations in the group not subject to the referral may be implemented if accepted by the reference Member State.

Once the variations have been accepted, within two months the competent authorities of the Member States concerned shall, where necessary, amend the marketing authorisation to reflect the variations, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the Member States concerned.

Variations relating to safety issues must be implemented immediately.

2.3.4. **Outcome of major variation of Type II assessment under the purely national procedure**

After receiving the holder's response, the national competent authority finalises its decision on the application and informs the holder as to whether the variation has been accepted or rejected, including the grounds for an unfavourable outcome.

Where several major variations of Type II, or a group of major variations of Type II with other minor variations, have been submitted as a single application, the national competent authority informs the holder which variations have been accepted or rejected. The holder may withdraw single variations from the group of variations during the procedure before the national competent authority has finalised its assessment.

After it has accepted the variation, within two months the competent authority of the Member State, where necessary, amends the marketing authorisation to reflect the variation, provided that it has received the documents necessary for the amendment of the marketing authorisation.

The accepted major variation of Type II may be implemented after the holder has been informed of the acceptance of the variation by the national competent authority, provided that the necessary documents to amend the marketing authorisation have been submitted.

Variations relating to safety issues must be implemented immediately.

2.3.5. **Major variation of Type II assessment under the centralised procedure**

Upon receiving a variation of Type II, the Agency handles the application as follows:

The Agency acknowledges receipt of a valid application of a major variation of Type II before the start of the procedure. The holder is informed of the timetable at the start of the procedure.

The Agency draws up an assessment report and an opinion on the application. During the procedure, the Agency may ask the holder to provide additional information, in which case the procedure is suspended until the information has been received.

The timelines for the Committee to assess responses depends on the complexity and amount of data to be provided to the holder. The timetable for assessment can be found on the Agency's website.

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

2.3.6. **Outcome of major variation of Type II assessment under the centralised procedure**

Once an opinion has been adopted, the Agency informs the holder within 15 days as to whether the opinion is favourable or unfavourable, including the grounds for an unfavourable opinion.

Where several major variations of Type II, or a group of major variations of Type II with other minor variations have been submitted as a single application, the Agency issues an opinion on the outcome of the procedure. That opinion includes a list of any variations not considered acceptable. The holder may withdraw single variations from the group of variations during the procedure before the Agency has adopted the opinion.

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

Where the opinion of the Agency is favourable and the variation affects the terms of the Commission decision granting the marketing authorisation, the Agency notifies the Commission of its opinion and the grounds for that opinion, and sends the necessary documents to amend the marketing authorisation.

Upon receiving the opinion and the relevant information, regarding the cases set out in Article 23(1a) of the Variations Regulation, the Commission amends the marketing authorisation within two months.

In the case of other variations, the Commission amends the decision granting the marketing authorisation within 12 months.

An accepted major variation of Type II requiring an amendment to the Commission decision granting the marketing authorisation within two months may only be implemented once the holder has been informed of the Commission decision. Where the amendment of the decision granting the marketing authorisation is not required within two months, or where the accepted variation does not affect the terms of that decision, the variation 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 immediately.

2.4. ***Extensions***

Annex I of the Variations Regulation sets out a list of changes to be considered as extensions. Under Article 19 of the Variations Regulation, such applications are evaluated in accordance with the same procedure for granting the initial marketing authorisation to which they refer. The extension may either be granted as a new marketing authorisation or included in the initial marketing authorisation to which it refers.

Extension applications must be submitted by the holder simultaneously to all relevant authorities.

Holders may group under a single application the submission of several extensions, or alternatively, group 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 where this has been agreed previously with the reference Member State, the national competent authority or the Agency, as applicable. No worksharing of extension applications is foreseen in the Variations Regulation.

2.5. *Annual update on human influenza and human coronavirus vaccines*

This section provides guidance on the application of Articles 12, 13f and 18 of the Variations Regulation to the annual update on human influenza vaccines.

A special 'fast track' variation procedure is available to deal with the annual change in active substances for the annual update of a human influenza vaccine and with a view to meeting the EU recommendation for human influenza virus strains vaccine composition for the coming season.

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

The 'fast track' procedure consists of two steps: the first is to assess the administrative and quality data elements, such as the summary of product characteristics, labelling and package leaflet, and the chemical, pharmaceutical, and biological documentation; the second is to evaluate any additional data.

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

Where relevant, an annual update procedure for human coronavirus vaccines will be laid down by the Agency. That procedure applies after an announcement published on the Agency's website. The announcement shall also mention the details of the procedure, including the timeframe for application.

Human influenza and coronavirus vaccines may be updated outside the annual procedure. In such cases, the relevant authority shall be contacted in advance to discuss this course of action, the data package (including Module 3 structure and content) and the timetable.

Furthermore, Article 21 of the Variations Regulation provides for a special urgent procedure for human influenza or human coronavirus pandemics, as recognised by the Commission, pursuant to Regulation (EU) 2022/2371 of the European Parliament and of the Council ([12]) (please see Section 2.6).

2.5.1. **Submission of variation applications for an 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 an annual update of human influenza vaccines under the mutual recognition procedure**

The reference Member State handles applications for an annual update as follows:

The reference Member State acknowledges receipt of a valid application within seven (7) days and informs the holder and the Member States concerned of the start of the procedure.

([12]) Regulation (EU) 2022/2371 of the European Parliament and of the Council of 23 November 2022 on serious cross-border threats to health and repealing Decision No 1082/2013/EU (OJ L 314, 6.12.2022, p. 26, ELI: http://data.europa.eu/eli/reg/2022/2371/oj).

The reference Member State prepares an assessment report and a decision on the application, considering first the administrative and quality data. The reference Member State must send the assessment and the draft decision within 45 days, as laid down in the Variations Regulation. Accordingly, in order to allow for sufficient time for the assessment of additional data (such as clinical and stability data) – the reference Member State is expected to conclude its assessment of the administrative and quality data within 30 days of receiving a valid application.

The reference Member State may ask the holder to provide additional information, such as clinical or stability data, in which case it informs the concerned Member States. When a request for additional information is sent to the holder, the procedure is suspended until the requested information has been received.

The reference Member State then sends its assessment report and draft decision to the concerned Member States. Within 12 days of receipt, the concerned Member States adopt a decision and inform the holder and the reference Member State of that decision.

2.5.3. **Variations assessment for an annual update of human influenza vaccines under the purely national procedure**

The national competent authority handles applications for an annual variation of human influenza vaccines as follows:

The national competent authority acknowledges receipt of a valid application of an annual variation human influenza vaccine and informs the holder.

During the evaluation period, the national competent authority may ask the holder to provide additional information, such as clinical or stability data, in which case the procedure is suspended until the requested information has been received.

Within 45 days of receiving a valid application, the national competent authority finalises the evaluation, including its decision on the application, and informs the holder as to whether the variation has been accepted or rejected, including the grounds for an unfavourable outcome.

2.5.4. **Variations assessment for an annual update of human influenza and human coronavirus vaccines under the centralised procedure**

The Agency handles applications for an application for an annual update of human influenza vaccines as follows:

The Agency acknowledges receipt of a valid application of an annual variation human influenza vaccine within seven days and informs the holder of the start of the procedure.

The Agency has up to 55 days, from the start of the procedure, to assess the application. It draws up an assessment report and an opinion on the application. The Agency may ask the holder to provide additional information, such as clinical or stability data, in which case the procedure is suspended until the requested information has been received.

Where necessary, based on the Agency's opinion, the Commission may amend the decision granting the marketing authorisation.

That procedure may be implemented in the case of a human coronavirus vaccine once an announcement has been published on the Agency's website. The announcement includes the details of the procedure, including the timetable for application. In the absence of such a dedicated procedure, any update of a human coronavirus vaccine should be processed in accordance with Section 2.6 below.

2.6. ***Human vaccines to address a potential or recognised public health emergency in the Union***

Under Annexes I and II to the Variations Regulation, updates may be made to the active substance of authorised human influenza vaccines, coronavirus vaccines or any other human vaccine that has the potential to address a public health emergency in the European Union.

As reflected in Annex II, such changes are classified as major variations of Type II.

Holders are advised to discuss the submission of such variations in advance with the Agency or, as applicable, the reference Member State or the national competent authority, in order to consider the appropriateness of the change to the active substance, taking into account (i) the epidemiological situation, (ii) the level of urgency, (iii) the data package including Module 3 structure and (iv) the timelines.

Any other variation to authorised human influenza vaccines, coronavirus vaccines or any other human vaccine that has the potential to address a public health emergency in the Union, that is not directly linked to the changes to the active substance follows the relevant variation procedures set out in other sections of the present guidelines. For coronavirus vaccines or any other human vaccine that has the potential to address a public health emergency in the Union, it may be permissible to add the active substance under the same marketing authorisation, subject to the agreement of the relevant authorities. This may lead to the co-existence of different versions of the vaccine (e.g. different serotypes, strains, antigens or coding sequences or combination of serotypes, strains, antigens, or coding sequences).

In order to ensure the appropriate differentiation of the different versions of the vaccine, and to facilitate traceability and pharmacovigilance monitoring, holders shall include qualifiers or abbreviations in the invented name. Furthermore, in the case of the above-mentioned co-existence, differentiation in the packaging of the different versions of the vaccine will be of paramount importance.

Under Article 21 of the Variations Regulation, during a public health emergency recognised by the Commission pursuant to Regulation (EU) 2022/2371, where certain pharmaceutical, non-clinical or clinical data are missing, the relevant authority may – by way of an exception and for a limited time – 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***

Under Article 22 of the Variations Regulation in the event of a risk to public health in the case of medicinal products, the holder may take provisional 'urgent safety restrictions'.

This means interim changes being made to the terms of the marketing authorisation due to new information that has a bearing on the safe use of the medicinal product. These urgent changes must subsequently be introduced via a corresponding variation in the marketing authorisation.

The holder must immediately notify all relevant authorities of the restrictions to be introduced.

If no objections have been raised by the relevant authority within 24 hours of receiving that information, the urgent safety restrictions are deemed to have been accepted. They must be implemented within a timeframe agreed between the reference Member State, the national competent authority or the Agency, and the holder.

Urgent safety restrictions may also be imposed by the Commission in relation to centrally authorised medicinal products or by the relevant authorities of the Member States in the event of a risk to public health related to medicinal products.

The corresponding variation application concerning the urgent safety restrictions, whether requested by the holder or imposed by the Commission or the relevant authorities of the Member States, must be submitted to all relevant authorities 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 ([13]) ('the Paediatric Regulation') provides for rewards upon receipt of the statement of compliance 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 the Paediatric Regulation, the holder of a supplementary protection certificate is entitled to a six-month extension of the period referred to in Regulation (EC) No 469/2009 of the European Parliament and of the Council ([14]) 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 the Paediatric Regulation, 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 of the European Parliament and of the Council ([15]) to 12 years under certain conditions, including the addition of the compliance statement to the marketing authorisation.

Where a medicinal product has been authorised, Article 23a of the Variations Regulation provides for a procedure to add a compliance statement to the marketing authorisation once the requirements provided in the Paediatric Regulation have been met. The compliance statement should be included in a relevant variation, e.g. submission of the results of PIP studies, following the PIP completion, to the relevant authority. Once it has been verified that all relevant conditions have been 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 provides the holder with confirmation that the compliance statement has been included in the technical dossier within 30 days of the conclusion of the relevant assessment.

3. PROCEDURAL GUIDANCE ON WORKSHARING

Under Article 20 of the Variations Regulation, holders are required to submit in a single application the same minor variation of Type IB, the same major variation of Type II, or the same group of variations corresponding to one of the cases listed in Annex III of the Variations Regulation or agreed with the reference Member State, the national competent authority or the Agency (as appropriate) which does not contain any extension, affecting several marketing authorisations in more than one Member State and owned by the same holder, granted via the national, mutual recognition, decentralised or centralised procedures, in any combination.

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') examines the variation on behalf of the other concerned authorities. Where at least one centralised marketing authorisation is concerned, the reference authority will be the Agency. If no centralised marketing authorisation is involved in worksharing, the reference authority is chosen by the holder. If none of the competent authorities proposed by the holder agrees to act as reference authority, the coordination group chooses the reference authority.

([13]) Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004 (OJ L 378 27.12.2006, p. 1, ELI: http://data.europa.eu/eli/reg/2006/1901/oj).

([14]) Regulation (EC) No 469/2009 of the European Parliament and of the Council of 6 May 2009 concerning the supplementary protection certificate for medicinal products (OJ L 152 16.6.2009, p. 1, ELI: http://data.europa.eu/eli/reg/2009/469/oj).

([15]) Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products (OJ L 18, 22.1.2000, p. 1, ELI: http://data.europa.eu/eli/reg/2000/141/oj).

In order to use a worksharing procedure, the same change shall apply to the different medicinal products concerned with no or limited need for assessment of any potential product-specific impact. Therefore, where the 'same' change to different marketing authorisations requires the submission of individual supporting data for specific medicinal products concerned or separate product-specific assessment, such changes cannot benefit from worksharing.

Where justified and agreed by the competent authorities of the Member States and the Agency, as applicable, holders may also choose to follow the worksharing procedure set out in this section 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 application under worksharing*

A variation or group of variations presented for worksharing must be submitted in the manner set out in Section 2 above and as one integrated submission package covering all variations for all medicinal products.

Worksharing applications must be submitted to all relevant authorities.

Worksharing procedures shall comply with the assessment period of the highest type of variation included.

3.2. *Worksharing assessment involving medicinal products other than those centrally authorised*

Where an upcoming worksharing procedure does not affect any centralised marketing authorisation, the holder informs the competent authority of the Member State preferred as reference authority before submitting the worksharing application. The chosen authority confirms that it agrees to act as the reference authority to the holder. Under the third subparagraph of Article 20(3) of the Variations Regulation, the coordination group may assign another relevant authority to assist the reference authority, if requested. If none of the competent authorities proposed by the holder agrees to act as the reference authority, the reference authority is chosen by the coordination group.

Upon receiving a worksharing application, the reference authority handles the application as follows:

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

The reference authority draws up a draft opinion according to that timetable and circulates it to the concerned Member States, and to the holder, for information. The concerned Member States then send their comments within the deadlines set out in the timetable.

As part of the procedure, the reference authority may ask the marketing authorisation holder to provide additional information, in which case the procedure is suspended until the information has been received.

3.3. *Outcome of the worksharing assessment involving medicinal products other than those centrally authorised*

Having received the holder's responses to the request for additional information, the reference authority finalises its opinion on the application and informs the concerned Member States and the holder.

In the case of a favourable opinion, a list of variations that are not considered acceptable are attached to the opinion. In the case of an unfavourable outcome, the grounds for that outcome should be explained.

Where applicable, the concerned Member States acknowledge the opinion within 30 days of receiving it and inform the reference authority, unless a potential serious risk to public health is identified that prevents a Member State from recognising the opinion of the reference authority. In such cases, the Member State in question shall inform the reference authority and give a detailed statement of the reasons for its position within 30 days of receiving the opinion.

The reference authority then refers the application to the coordination group for applying Article 29(3), (4) and (5) of Directive 2001/83/EC to the in matters on which there is disagreement and informs the holder and the Member States concerned accordingly. The holder is not entitled to initiate such a referral.

Where a referral to the CMDh is made, the procedure concerning the decision on the worksharing application is suspended until a decision has been adopted on the referral procedure. This also applies to referrals to the Committee under Articles 32 to 34 of Directive 2001/83/EC.

Within 30 days of the approval of the opinion or, where a referral has been initiated, the notification of the agreement of the coordination group or the Commission decision, as applicable, the Member States concerned amend the marketing authorisation accordingly, provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the Member States concerned.

A minor variation of Type IB accepted in a worksharing procedure may be implemented once the reference authority has issued a favourable opinion.

Major variations of Type II, including those containing grouped minor variations of Type IB, and accepted in 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 cases where the application has been the object of a referral, the variation must not be implemented until the referral procedure has concluded that the variation has been accepted.

3.4. ***Worksharing assessment involving centrally authorised medicinal products***

When an upcoming worksharing procedure affects a centralised marketing authorisation, the holder informs the Agency before submitting the worksharing application.

Upon receiving a worksharing application that affects at least one centralised marketing authorisation, the Agency handles the application as follows:

The Agency acknowledges receipt of a valid worksharing application and starts the procedure immediately. The holder is informed of the adopted timetable at the start of the procedure.

The Agency appoints a rapporteur, and in some cases also a co-rapporteur, to lead the procedure.

During the procedure, the Agency may request additional information, in which case the procedure is suspended until this information has been received. An oral explanation may be held at the request of the relevant Committee or the marketing authorisation holder, where appropriate.

3.5. ***Outcome of the worksharing assessment involving centrally authorised medicinal products***

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

Where the Agency's opinion is favourable and the variation affects the terms of the Commission decision granting the marketing authorisation, the Agency sends the Commission its opinion and the grounds for its opinion along with any necessary documents to amend the marketing authorisation.

If the Agency considers that some variations are not acceptable, the list of variations that are not considered acceptable should be attached to the opinion. Variations may be considered acceptable for some of the medicinal products in question.

Upon receiving a favourable opinion by the Member States concerned or the Commission, the following steps are taken:

— 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 variations of Type IB, except those grouped with major variations of Type II, may be implemented upon receiving a favourable opinion from the Agency.

Major variations of Type II, and minor variations of Type IB grouped with a major variation of Type II may be implemented 30 days after receiving a favourable opinion from the Agency provided that the documents necessary for the amendment of the marketing authorisation have been submitted to the Member States concerned, and the application has not been the object of a referral.

— For centrally authorised medicinal products, upon receipt of the opinion and the relevant information, the Commission amends the marketing authorisation within two months in the cases set out in Article 23(1a) of the Variations Regulation. In the case of other variations, the Commission amends the decision granting the marketing authorisation within 12 months.

Minor variations of Type IB, except those grouped with major variations of Type II, may be implemented upon receipt of a favourable opinion of the Agency.

Major variations of Type II, and minor variations of Type IB grouped with a major variation of Type II, except variations that require the adoption of a Commission decision within two months, may be implemented 30 days after receipt of a 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: E) Administrative changes; Q) Quality changes; C) Safety, Efficacy and Pharmacovigilance changes and M) Specific changes to Plasma Master Files and Vaccine Antigen Master Files.

Where reference is 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. E, Q, C or M),

— 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 variation of Type IA or major variation of Type II in accordance with the definitions of Article 2 and Annex II to the Variations Regulation. It also indicates which minor variations of Type IA require immediate notification pursuant to Articles 8(1), 13a(1) and 14(1) of the Variations Regulation.

— A list of variations to be considered as minor variation of Type IB. In accordance with Article 3 of the Variations Regulation, this category applies by default. Accordingly, this Annex does not claim to be an exhaustive list for this category of variations.

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

When one or more of the conditions laid down in this Annex for a minor variation of Type IA are not met, the concerned change may be submitted as a minor variation of Type IB ('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 major variation of Type II.

For the purpose of this Annex, 'test procedure' has the same meaning as 'analytical procedure'; 'limits' has the same meaning as 'acceptance criteria'; 'specification attribute' 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 attribute therefore includes its corresponding test method and limits.

Where several minor changes are taking place at the same time, e.g. to the same method or process or material, 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 in their choice of the appropriate classification and submit the changes accordingly.

As regards the data package, the relevant supporting data for minor variations of Type IB and major variations of Type II will depend on the specific nature of the change.

In the event of a change in the therapeutic indication, posology or maximum daily dose, the quality documentation should be reviewed. Any resulting change to the quality documentation, e.g. the need to change impurity limits, will require the submission of the appropriate quality variation under chapter Q of this Annex.

Furthermore, if a variation leads to a revision of the product information, this change is considered part of that variation. In such cases, updated product information must be submitted as part of the application, along with translations. Mock-ups or specimens should be provided to the Member States concerned, the national competent authority or the Agency, as applicable.

Where reference is made to the 'current edition' in the dossier of an authorised medicinal product, 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. Holders are reminded that compliance with the updated monograph should be implemented within six (6) months.

References in the Annex to monographs of the European Pharmacopoeia are only applicable to active substance or excipient monographs 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.

Under Part III, point 1 of Annex I to Directive 2001/83/EC, changes to Plasma Master Files (PMFs) and Vaccine Antigen Master Files (VAMFs) follow the evaluation procedures for variations set out in the Variations Regulation. Chapter M of this Annex provides a list of variations that are specific to such PMFs or VAMFs. Following a review of these variations, any marketing authorisation concerned must be updated in accordance with Chapter Q.V. of this Annex. In cases where 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 be handled in accordance with this Annex.

References in this Annex to changes to the marketing authorisation dossier mean addition, replacement or deletion, unless otherwise indicated. If amendments to the dossier are merely editorial changes, such changes should generally not be submitted as a separate variation. However, they may be included in a variation concerning that part of the dossier. In such cases, the changes should be clearly identified in the application form: editorial changes should be made along with a statement indicating that the content of the part of the dossier in question has not been changed by the editorial changes beyond the scope of the variation submitted. It should be noted that editorial changes include the removal of obsolete or redundant text but not the removal of specification attributes or manufacturing descriptions.

Additional information:

— Commission Regulation (EC) No 1234/2008

— EMA Procedural Guidance on Variations

— CMDh Procedural Guidance on Variations

ANNEX

E. ADMINISTRATIVE CHANGES

E.1

E.1	**Change in the (invented) name of the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	for centrally authorised medicinal products	1	1, 2	IA_{IN}
(b)	for nationally authorised medicinal products		2	IB

Conditions

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

E.1	**Change in the (invented) name of the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	Documentation			
	1. Copy of the EMA letter of acceptance of the new (invented) name.			
	2. Revised product information.			

E.2

E.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	IA_{IN}
	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 and/or declaration of conformity, if available.			
	2. Revised product information, as appropriate.			
	3. Amendment of the relevant section(s) of the dossier.			

E.3

E.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.			

E.4

E.4	**Change in the name and/or address of the marketing authorisation holder, ASMF holder, storage site of the master and/or working cell bank, 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	IA_{IN}
(b)	The change in the name and/or address concerns a manufacturer(s) whose activities include batch release of the finished product	1	1, 2	IA_{IN}
(c)	The change in the name and/or address does not concern a manufacturer(s) whose activities include batch release of the finished product 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 competent authority) 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'.

E.5

E.5	**Deletion of manufacturing sites for an active substance, intermediate or finished product, storage of master and/or working cell bank, 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.

Q. QUALITY CHANGES

Q.I **Active substance**

Q.I.a) ***Manufacture***

Q.I.a.1

Q.I.a.1	**Change in the manufacturing site of a starting material/intermediate used in the manufacturing process of the active substance or change in the manufacturing site (including where relevant quality control testing sites) of the active substance**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
Manufacturing site of an active substance or starting material or intermediate				
(a)	Addition or replacement of a manufacturing site of an active substance or intermediate	1, 2, 3	1, 2, 3, 4, 5, 6	IA_{IN}
(b)	Addition or replacement of a manufacturing site 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 manufacturing site of a starting material used in the manufacture of the active substance or reagent required to be mentioned in the dossier	1, 2, 3	1, 2, 3, 4, 6	IA
(d)	Addition or replacement of a manufacturing site of — a biological active substance or — a biological starting material/reagent/raw material/intermediate used in the manufacture of a biological active substance which may have a significant impact on the quality, safety or efficacy of the finished 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 manufacturing site using the same or different plant production (i.e. cultivated or wild collection)		1, 4, 5, 6, 7, 8	IB
(f)	Addition of a manufacturing site of the active substance that is supported by an Active Substance Master File (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, 4	1, 4, 5	IA

Q.I.a.1	**Change in the manufacturing site of a starting material/intermediate used in the manufacturing process of the active substance or change in the manufacturing site (including where relevant quality control testing sites) of the active substance**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
Quality control testing arrangements for the active substance or starting material or intermediate				
(i)	Addition or replacement of a batch control/testing site of the active substance or starting material/intermediate used in the manufacturing of a biological active substance, applying a biological/immunological/immunochemical analytical procedure		1, 9, 10	IB
(j)	Addition or replacement of a batch control/testing site of the — the active substance or — intermediate of an active substance or — starting material of a biological active substance applying physicochemical and/or microbiological analytical procedures	5, 6	1	IA
Other				
(k)	Addition or replacement of a storage site of the Master Cell Bank and/or Working Cell Banks	7	1	IA

Conditions

1. For starting materials, the specifications and analytical procedures are identical to those already approved.
For intermediates and active substances the specifications (including in process controls, analytical procedures), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved.
For herbal active substances, 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.

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

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

5. Method transfer from the old to the new site has been successfully completed.

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 format).

2. A declaration from the marketing authorisation holder (and the ASMF holder, where applicable) that the starting material (specifications and analytical procedures) and that the synthetic route, quality control procedures and specifications of the active substance and of the intermediate used 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.

Q.I.a.1	**Change in the manufacturing site of a starting material/intermediate used in the manufacturing process of the active substance or change in the manufacturing site (including where relevant quality control testing sites) of the active substance**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	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/starting material 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 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 Q.II.b.1).			
	6. Where relevant, a commitment of the manufacturer of the active substance to inform the marketing authorisation 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. Valid proof that the proposed site is GMP compliant for the manufacturing and/or testing operation(s) concerned: — For a site within the EU/EEA: a copy of the current manufacturing authorisation 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 third country site where a GMP mutual recognition agreement (MRA) or other relevant agreement on GMP is in place between the country concerned and the EU: a proof of GMP compliance issued within the last 3 years by the relevant local competent authority. — For a third country site where no MRA or relevant agreement on GMP is in place: a GMP certificate issued within the last 3 years by an EEA Member State. 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).			

Q.I.a.2

Q.I.a.2	**Change in the manufacturing process of the active substance, intermediate of an active substance or starting materials for biological active substance**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Minor change in the manufacturing process	1, 2, 3, 4, 5	1, 2, 3, 4	IA
(b)	Major change to the manufacturing process which may have a significant impact on the quality, safety or efficacy of the finished product			II
(c)	Change in the geographical source of a herbal starting material and/or production of a herbal substance		1, 2, 3, 4, 5	IB
(d)	Minor change to the restricted part of an Active Substance Master File		1, 2, 3, 6	IB
(e)	Deletion of a manufacturing process	6, 7	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: 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. 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.	The change does not result from unexpected events arising during manufacture or because of stability concerns, and is not as a result of a safety or quality issue.
6.	The deletion should not be due to critical deficiencies concerning manufacturing.
7.	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 comparative tabular format) of at least two batches (minimum pilot scale), of the active substance or intermediate as appropriate, manufactured according to the currently approved and proposed process.
3.	Copy of approved specifications of the active substance (as annex to the application form).

Q.I.a.2	**Change in the manufacturing process of the active substance, intermediate of an active substance or starting materials for biological active substance**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	4. A declaration from the marketing authorisation holder that an evaluation has been performed and the minor changes do not impact the quality, safety or efficacy of the active substance/finished 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 (e.g. for extracts: extraction time, temperature, pressure).			
	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 (and the ASMF holder, where applicable) that there is no change in qualitative and quantitative impurity profile or in physico-chemical properties, that the synthetic route remains the same and that the specifications of the active substance or intermediates are unchanged.			
Note for Q.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.			

Q.I.a.3

Q.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, 5, 6, 7	1, 2, 3	IA
(b)	Downscaling of the approved batch size	1, 2, 3, 4, 5, 6, 8	1, 2, 3	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, 4	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.			
	4. The change does not adversely affect the reproducibility of the process.			
	5. The change is fully described in the open ('applicant's') part of an Active Substance Master File, if applicable.			
	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.			

Q.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
	8. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
	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. 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.			
	4. For biological active substance, a justification that an assessment of comparability is not required.			

Q.I.a.4

Q.I.a.4	**Change to in-process controls applied during the manufacture of the active substance, intermediate of an active substance or starting materials for biological active substance**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	(a) Minor change of in-process control limits	1, 2, 3, 4, 5	1, 2	IA
	(b) Addition of new in-process control and limits with its corresponding analytical procedure	1, 2, 5, 6	1, 2, 3, 4, 5	IA
	(c) Deletion of a non-significant or obsolete in-process control	1, 2, 5, 7, 8	1, 2, 6	IA
	(d) Widening of the approved in-process control 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) Change of an analytical procedure for an in-process control	2, 4, 5, 9, 10	1	IA
	(g) Replacement of an in-process control 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 in-process control 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.			

Q.I.a.4	**Change to in-process controls applied during the manufacture of the active substance, intermediate of an active substance or starting materials for biological active substance**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	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. The change is fully described in the open ('applicant's') part of an Active Substance Master File, if applicable.			
	6. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.			
	7. The in-process control 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. The change is not related to a revision of the control strategy with an intention to minimise testing of parameters and attributes (critical or non-critical).			
	9. The new analytical procedure is not a biological/immunological/immunochemical procedure.			
	10. 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 controls and limits.			
	3. Details of any new non-pharmacopoeial analytical method and validation data, where relevant.			
	4. Batch analysis data on two production batches of the active substance for all specification attributes.			
	5. Justification from the holder or ASMF holder as appropriate for the new in-process control and limits.			
	6. Justification/risk assessment from the marketing authorisation holder or the ASMF holder, as appropriate, that the in-process controls are non-significant, or that the in-process controls are obsolete.			

Q.I.a.5

Q.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

Q.I.a.6

Q.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, 4	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.	Amendment of the relevant section(s) of the dossier, as appropriate.			
3.	Declaration that the serotype, strain, antigen or coding sequence is no longer appropriate in relation to the epidemiological evolution of the human virus of concern.			
4.	Revised product information.			

Q.I.b) ***Control of active substance***

Q.I.b.1

Q.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 specification acceptance criteria for finished product subject to Official Control Authority Batch Release	1, 2, 3	1, 2	IA_{IN}
(b)	Change within the specification acceptance criteria	1, 2, 3, 4	1, 2	IA
(c)	Addition of a new specification attribute with its corresponding analytical procedure and acceptance criteria	1, 2, 4, 5, 6	1, 2, 3, 4, 5	IA
(d)	Deletion of a non-significant or an obsolete specification attribute	1, 2, 4, 7, 8	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 specification acceptance criteria for the active substance			II
(g)	Change outside of the 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

Q.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
(h)	Change outside of the specification acceptance criteria for starting material/reagent/intermediate		1, 2, 4, 5	IB
(i)	Change in specification attribute for the active substance from in-house to a non-official Pharmacopoeia/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	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, 5	IB
(k)	Change in the testing of specification attribute of the active substance, from routine to skip/periodic testing and vice versa		1, 2, 7	IB
(l)	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 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.	The analytical procedure remains the same.
4.	The change is fully described in the open ('applicant's') part of an Active Substance Master File, if applicable.
5.	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.
6.	Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.
7.	The change is not related to a revision of the control strategy with an intention to minimise testing of parameters and attributes (critical or non-critical).
8.	The specification attribute does not concern a critical attribute, for example: — identity test, — assay, — purity, — impurities (except when a solvent is no longer used in the manufacture of the active substance), — a critical physical characteristics (for example: polymorphism, particle size, bulk or tapped density), — 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.

Q.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
	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. Justification from the marketing authorisation holder or ASMF holder as appropriate of the new specification attribute and the acceptance criteria.			
	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 marketing authorisation holder or the ASMF holder for the change in the testing of specification attribute. A change from routine testing to skip/periodic testing is warranted when the manufacturing process is under control and supported by sufficient amount of historical data compliant with the specification or as foreseen by relevant guidelines. A change from skip/periodic testing to routine testing should be supported by analytical data demonstrating failure to meet the approved acceptance criteria for the skip tested specification.			

Q.I.b.2

Q.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, 4	1, 2	IA
	(b) Deletion of an analytical procedure for the active substance if an alternative procedure is already authorised	4, 5	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	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, 4	1, 2	IA
	(f) Deletion of an analytical procedure for a starting material/reagent/intermediate, if an alternative analytical procedure is already authorised	4, 5	1	IA
	(g) Introduction, replacement or 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, 4, 6, 7	1, 2	IA

Q.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
	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 change is fully described in the open ('applicant's') part of an Active Substance Master File, if applicable.			
	5. An alternative analytical procedure is already authorised for the specification attribute.			
	6. Any new analytical procedure does not concern a novel non-standard technique or a standard technique used in a novel way.			
	7. The analytical procedure is not a biological/immunological/immunochemical procedure.			
	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.			
	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.			

Q.I.b.3

Q.I.b.3	**Change to an in-house reference standard/preparation for a biological active substance**	Condition to be fulfilled	Documen-tation 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 or 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			II

Q.I.b.3	**Change to an in-house reference standard/preparation for a biological active substance**	Condition to be fulfilled	Documentation to be supplied	Procedure type
(e)	Other change to the qualification protocol for the prepartation/ replacement of an in-house reference standard or preparation		1	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.			

([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 or the extension of its re-test period/storage period, 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 as long as all approved acceptance criteria are met.

Q.I.c) ***Container closure system***

Q.I.c.1

Q.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 non-liquid active substance	1, 2, 3	1, 2, 3, 4	IA
(b)	Change in immediate packaging of sterile liquid active substance			II
(c)	Change in immediate packaging of nonsterile liquid active substance		1, 2, 4, 5	IB
(d)	Deletion of one of the authorised immediate packagings of the active substance	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 or biological active substance.			
4.	There should be at least one remaining packaging adequate for the storage of the active substance at the authorised conditions.			

Q.I.c.1	**Change in immediate packaging of the active substance**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	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). Where appropriate, proof must be provided that no interaction between the content and the packaging material has no impact on the active substance quality (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.			
	3. 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).			
	4. Comparison of the current and proposed immediate packaging specifications, if applicable.			
	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).			

Q.I.c.2

Q.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)	Change 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, 4	IA
(c)	Deletion of a non-significant or obsolete specification attribute	1, 2, 6	1, 2, 5	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 because of stability concerns during storage of the active substance, 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.			

Q.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
	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 is not related to a revision of the control strategy with an intention to minimise testing of parameters and attributes (critical or non-critical).			
	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 from the marketing authorisation holder or the ASMF Holder, as appropriate, of the new specification attribute and the acceptance criteria.			
	5. Justification/risk assessment from the marketing authorisation holder or the ASMF Holder, as appropriate, that the specification attribute is non-significant, or obsolete.			

Q.I.c.3

Q.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	4	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 an analytical procedure registered for the specification attribute.			
	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.			

Q.I.c.4

Q.I.c.4	**Change of a secondary packaging component of the active substance (including replacement, addition or deletion), 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 because of stability concerns during storage of the active substance.			
	Documentation			
	1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

Q.I.d) ***Stability***

Q.I.d.1

Q.I.d.1	**Change in the re-test period/storage period or storage conditions of the active substance or intermediates used in the manufacturing process of the biological 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	1	1, 2, 3, 4	IA
	2. Introduction of re-test period/storage period		1, 2, 3	IB
	3. Extension of the re-test period/storage period based on extrapolation or stability modelling not in accordance with relevant stability guidelines			II
	4. Extension of re-test period/storage period 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 supported by real time data fully in line with the stability protocol	2	1, 2, 3	IA
	(b) Storage conditions			
	1. Change to more restrictive storage conditions	1, 3	1, 2, 3	IA
	2. Change in storage conditions		1, 2, 3	IB
	(c) Change to an approved stability protocol	1, 4	1, 4	IA

Q.I.d.1	**Change in the re-test period/storage period or storage conditions of the active substance or intermediates used in the manufacturing process of the biological active substance**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	Conditions			
	1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
	2. 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 unexpected trends have been observed.			
	3. The physical state of the active substance has not changed.			
	4. The changes do not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.			
	Documentation			
	1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format). This must contain results of appropriate real time stability studies, conducted in accordance with the relevant stability guidelines on three pilot or production scale batches of the active substance or intermediate in the authorised packaging material.			
	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 (as annex to the application form).			
	4. Justification for the proposed changes.			

Q.I.e) ***Additional regulatory tools***

Q.I.e.1

Q.I.e.1	**Introduction of a new design space (method operable design range (MODR)) 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 for an analytical procedure for a starting material/reagent/intermediate and/or the active substance		1, 2, 3	IB
	(c) Changes to, or extension of, an approved design space for the active substance and/or an analytical procedure for a starting material/ reagent/intermediate		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.			

Q.I.e.1	**Introduction of a new design space (method operable design range (MODR)) or extension of an approved design space for the active substance**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	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).			

Q.I.e.2

Q.I.e.2	**Introduction of a post-approval change management protocol (PACMP) 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. Post-approval change management protocol related to the active substance.			
	3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

Q.I.e.3

Q.I.e.3	**Deletion of a post-approval change management protocol (PACMP) 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 post-approval 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).			

Q.I.e.4

Q.I.e.4	**Changes to a post-approval change management protocol (PACMP)**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	(a) Major changes to a post-approval change management protocol			II
	(b) Minor changes to a post-approval 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.			

Q.I.e.5

Q.I.e.5	**Implementation of changes foreseen in a post-approval change management protocol (PACMP)**	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, 3	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 post-approval change management protocol which requires its notification within 12 months following implementation.

2. The proposed change has been performed fully in line with the post-approval change management protocol, which requires its immediate notification following implementation.

Documentation

1. Reference to the post-approval change management protocol.

2. Declaration that the change is in accordance with the post-approval change management protocol and that the study results meet the acceptance criteria specified in the protocol (*)

3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).

4. Results of the studies performed in accordance with the post-approval change management protocol.

(*) 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.

Q.I.e.6

Q.I.e.6	**Introduction of a product lifecycle management document (PLCM) 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).

Q.I.e.7

Q.I.e.7	**Changes related to the active substance in line with an approved product lifecycle management document (PLCM)**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Major change to the active substance in line with an approved PLCM		1, 2, 3	II
(b)	Minor change to the active substance in line with an approved PLCM	1	1, 2, 3	IA
(c)	Minor change to the active substance in line with an approved PLCM	2	1, 2, 3	IA_{IN}
(d)	Minor change to the active substance in line with an approved PLCM		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 (PLCM) with relevant sections modified.
3.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).

Q.I.e.8

Q.I.e.8	**Changes to an approved product lifecycle management document (PLCM) related to the active substance**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Major changes to an approved PLCM			II
(b)	Minor changes to an approved PLCM		1, 2, 3	IB

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 (PLCM) with relevant sections modified.
3.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).

Q.II. **Finished product**

Q.II.a) ***Description and composition***

Q.II.a.1

Q.II.a.1	**Change or addition of imprints, bossing (embossing/debossing) 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 (embossing/debossing) 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.			

Q.II.a.2

Q.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 shape or 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.			

Q.II.a.2 **Change in the shape or dimensions of the pharmaceutical form**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
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 Q.II.a.2.c Applicants are reminded that any change to the 'strength' of the finished product requires the submission of an Extension application.			

Q.II.a.3

Q.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 finished product (for example, biological excipients or a 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			II
4. Replacement of excipient(s) with 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).			

Q.II.a.3 **Change in the composition (excipients) of the finished product**		Cond. to be fulfilled	Docum. to be supplied	Proced. type
2.	Any minor adjustment to the formulation to maintain the total weight should be made by one or more excipient(s) which currently make(s) 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 Union legislation (e.g. Regulation (EC) No 1333/2008 of the European Parliament and of the Council ([1]), Commission Regulation (EU) No 231/2012 ([2]) on food additives and Regulation (EC) No 1334/2008 of the European Parliament and of the Council ([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 finished 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).			

Q.II.a.3	**Change in the composition (excipients) of the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
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]) Regulation (EC) No 1333/2008 of the European Parliament and of the Council of 16 December 2008 on food additives (OJ L 354, 31.12.2008, p. 16, ELI: http://data.europa.eu/eli/reg/2008/1333/oj).

([2]) Commission Regulation (EU) No 231/2012 of 9 March 2012 laying down specifications for food additives listed in Annexes II and III to Regulation (EC) No 1333/2008 of the European Parliament and of the Council (OJ L 83, 22.3.2012, p. 1, ELI: http://data.europa.eu/eli/reg/2012/231/oj).

([3]) Regulation (EC) No 1334/2008 of the European Parliament and of the Council of 16 December 2008 on flavourings and certain food ingredients with flavouring properties for use in and on foods and amending Council Regulation (EEC) No 1601/91, Regulations (EC) No 2232/96 and (EC) No 110/2008 and Directive 2000/13/EC (OJ L 354, 31.12.2008, p. 34, ELI: http://data.europa.eu/eli/reg/2008/1334/oj).

Q.II.a.4

Q.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 or capsule shell is a critical factor for the release mechanism		1, 3, 4, 5, 6	IB
(c)	Modified or prolonged release pharmaceutical forms where the coating or capsule shell 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 or for the control of other quality attribute(s).			
3.	The finished product specification has only been updated in respect of weight and dimensions, if applicable.			

Q.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
	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. For herbal medicinal products where dissolution testing may not be feasible, comparative disintegration data should be provided.			
	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.			

Q.II.a.5

Q.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

Q.II.a.6

Q.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 finished product.			
	2. Revised product information.			

Q.II.b) ***Manufacture***

Q.II.b.1

Q.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 immediate 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 finished product manufactured by novel or 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) of a finished product		1, 2, 4, 5, 6, 7, 8	IB
(f)	Addition or replacement of a site responsible for the assembly of a finished product containing 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, 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. Valid proof that the proposed site is GMP compliant for the manufacturing and/or testing operation(s) concerned:
   - 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 third country site where a GMP mutual recognition agreement (MRA) or other relevant agreement is in place between the country concerned and the EU: a proof of GMP compliance issued within the last 3 years by the relevant local competent authority;
   - For a third country site where no MRA or relevant agreement on GMP is in place: a GMP certificate issued within the last 3 years by an EEA Member State 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 (as annex to the application form).

Q.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
	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 appropriate imaging technique.			
	6. (i) If the new manufacturing site uses the active substance as a starting material – A declaration by the qualified person 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 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 immediate 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 of Directive 2001/83/EC, manufacture includes complete or partial manufacture, import, dividing up, packaging or presentation prior to its incorporation into a finished 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 (Directive 2002/98/EC of the European Parliament and of the Council of 27 January 2003 setting standards of quality and safety for the collection, testing, processing, storage and distribution of human blood and blood components and amending Directive 2001/83/EC (OJ L 33, 8.2.2003, p. 30, ELI: http://data.europa.eu/eli/dir/2002/98/oj)).

Q.II.b.2

Q.II.b.2	**Change to batch release arrangements and batch control testing of the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Addition or replacement of a batch control/testing site applying physicochemical and/or microbiological analytical procedures for the finished product	2, 3, 4, 5	1, 4	IA
(b)	Addition or replacement of a batch control/testing site applying a biological/immunological/immunochemical analytical procedure for a biological finished product		1, 4, 5	IB
(c)	Addition or replacement of a site responsible for batch release (QP certification)			
	1. Not including batch control/testing	1, 2, 5	1, 2, 3, 4, 6	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 6	IA_{IN}
	3. Including batch control/testing applying a biological/immunological/immunochemical analytical procedure for a biological finished product		1, 2, 3, 4, 5, 6	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.

Q.II.b.2	**Change to batch release arrangements and batch control testing of the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	Documentation			
1.	Valid proof that the proposed site is GMP compliant for the manufacturing and/or testing operation(s) concerned: — For a site within the EU/EEA: a 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 third country site where a GMP mutual recognition agreement (MRA) or other relevant agreement on GMP is in place between the country concerned and the EU: a proof of GMP compliance, issued within the last 3 years by the relevant local competent authority. — For a third country site where no MRA or relevant agreement on GMP is in place: a GMP certificate issued within the last 3 years by an EEA Member State. A reference to the EudraGMP database will suffice.			
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. Q.II.b.1).			
4.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format), 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).			
6.	Revised product information.			

Q.II.b.3

Q.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, 8	1, 2, 3, 4, 5, 6, 7, 8, 9	IA
(b)	Major change to a manufacturing process of the finish product that may have a significant impact on the quality, safety and efficacy of the finished product			II
(c)	Introduction of a non-standard terminal sterilisation method			II
(d)	Introduction of, or change in, an overage that is used for the active substance			II
(e)	Change in the holding time and/or storage conditions of an intermediate or bulk product used in the manufacture of the finished product		1, 6, 10	IB

Q.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
	Conditions			
	1. No change in qualitative and quantitative impurity profile or in physico-chemical properties.			
	2. The change relates to immediate release oral pharmaceutical forms or to non-sterile solutions or the change relates to non-critical process parameter(s), i.e. process parameter(s) that, in the context of a previous assessment by the competent authority, 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. 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).			
	8. The change does not result from unexpected events arising during manufacture or because of stability concerns, and is not as a result of a safety or quality issue.			
	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 (as annex to the application form).			
	7. Batch analysis data (in a comparative tabulated format) on a minimum of two batches manufactured to both the currently approved and the proposed process.			

Q.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
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. 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 an evaluation of the concerned manufacturing step(s) has been performed and the minor change does not impact the quality, safety or efficacy of the finished product.			
10.	Data to validate the proposed change in holding time and/or storage conditions of the intermediate or bulk product (minimum of two batches at pilot or commercial scale). 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.			

Q.*II.b.4*

Q.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	IA
(b)	Downscaling down to 10-fold	1, 2, 3, 4, 5, 6	1, 3	IA
(c)	The change requires assessment of the comparability of a biological finished product or the change in batch size requires a new bioequivalence study			II
(d)	The change relates to all other pharmaceutical forms manufactured by novel or complex manufacturing processes			II
(e)	More than 10-fold increase/decrease compared to the originally approved batch size		1, 2, 3, 4, 5, 6	IB
(f)	The scale for a biological finished product is increased/decreased without process change (e.g. duplication of line)		1, 2, 3, 4, 5, 6	IB
	Conditions			
1.	The change does not affect reproducibility and/or consistency of the product.			
2.	The change relates to immediate release oral pharmaceutical forms or to non-sterile solutions.			
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.			

Q.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
	5. The product concerned is not a biological finished product.			
	6. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
	7. The batch size is within the 10-fold range of the batch size foreseen when the marketing authorisation was granted or following a subsequent change not agreed as a Type IA variation.			
	Documentation			
	1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			
	2. Batch analysis data (in a comparative tabulated format) on a minimum of 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. 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.			
	4. The validation results should be provided.			
	5. 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).			
	6. For biological finished products, a justification that an assessment of comparability is not required.			

Q.II.b.5

Q.II.b.5	**Change to in-process control 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 control limits	1, 2, 3, 4	1, 2	IA
(b)	Addition of new in-process control 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 control	1, 2, 7, 9	1, 2, 5	IA
(d)	Deletion of an in-process control which may have a significant effect on the overall quality of the finished product			II
(e)	Widening of the approved in-process control limits, which may have a significant effect on overall quality of the finished product			II
(f)	Change of an analytical procedure for an in-process control	2, 4, 6, 8	1, 7	IA
(g)	Replacement of an in-process control with its corresponding analytical procedure		1, 2, 3, 4, 5	IB

Q.II.b.5	**Change to in-process control or limits applied during the manufacture of the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	Conditions			
1.	The change is not a consequence of any commitment from previous assessments to review in-process control (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 or because of stability concerns, 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 control does not concern the control of a critical attribute for example: — assay, — purity, — impurities (except solvent is no 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.			
9.	The change is not related to a revision of the control strategy with an intention to minimise testing of parameters and attributes (critical or non-critical).			
	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 control and limits.			
3.	Details of any new analytical procedure and validation data, where relevant.			
4.	Batch analysis data on two production of the finished product for all specification attributes.			
5.	Justification/risk assessment showing that the in-process control is non-significant or that it is obsolete.			
6.	Justification of the new in-process control and limits.			
7.	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.			

Q.II.c) ***Control of excipients***

Q.II.c.1

Q.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, 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, 7	IA
(c)	Deletion of a non-significant or obsolete specification attribute	1, 2, 3, 7	1, 2, 6	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 of an excipient from in-house to a non-official Pharmacopoeia/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
(g)	Replacement of a specification attribute with its corresponding analytical procedure		1, 2, 3, 4, 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).
2.	The change does not result from unexpected events arising during manufacture or because of stability concerns and is not as a result of a safety or quality issue, e.g. new unqualified impurity; change in total impurity limits.
3.	The change is not related to a revisions of the control strategy with an intention to minimise redundant testing of parameters and attributes (critical or non-critical).
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 critical attribute, for example: — assay, — purity, — impurities (except when a solvent is no longer used in the manufacture of the excipient), — a critical physical characteristic (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).

Q.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
	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 of the excipient for all specification attributes [3 production batches (unless otherwise justified) for biological excipients or novel excipients].			
	5. Justification for not submitting a new bioequivalence study according to the relevant Guideline on The Investigation of Bioequivalence, if appropriate.			
	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.			

Q.II.c.2

Q.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 analytical procedure is already authorised	4	1	IA
(c)	Introduction, replacement or substantial change to a biological/immunological/immunochemical analytical procedure for an excipient			II
(d)	Other changes to an 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. An alternative analytical procedure is already authorised for the specification attribute.			
	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.			
	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.			

Q.II.c.3

Q.II.c.3	**Change in source of an excipient or reagent with TSE risk, which is used in the manufacture of an active substance or in a finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Change in the source of an excipient or reagent from a TSE risk material to a material of vegetable or synthetic origin	1	1, 2, 3	IA
(b)	Change in the source of an excipient or reagent which is unlikely to present any risk of TSE contamination	1, 2	1, 3	IA
(c)	Change in the source of a TSE risk material, or introduction of a TSE risk material, not covered by a European Pharmacopoeial TSE certificate of suitability			II

Conditions

1.	Excipient and finished product release and end of shelf life specifications remain the same.
2.	Compliance with the conditions formulated in the *Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products* has to be ensured.

Documentation

1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format.
2.	Declaration from the manufacturer or the marketing authorisation holder of the material that it is purely of vegetable or synthetic origin.
3.	Confirmation of equivalence of the materials and that there is no impact on the quality of the finished product.

Q.II.c.4

Q.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, when 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.

Q.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
	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 (as annex to the application form).			

Q.II.d) ***Control of finished product***

Q.II.d.1

Q.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, 4	1, 2	IA
(b)	Change within the specification acceptance criteria for finished products subject to Official Control Authority Batch Release	1, 2, 4	1, 2	IA_{IN}
(c)	Addition of a new specification attribute with its corresponding analytical procedure and acceptance criteria	1, 2, 5, 6	1, 2, 3, 4, 6	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, 2, 3, 7	1, 2, 5	IA
(e)	Change outside of the 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 (*).	1, 2, 4, 6	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, 8	1, 2, 4	IA

Q.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
(i)	Change in the testing of specification attribute, from routine to skip/periodic testing and vice versa		1, 2, 7	IB
(j)	Replacement of a specification attribute with its corresponding analytical procedure		1, 2, 3, 4, 6	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 because of stability concerns, or as a result of a safety or quality issue, e.g. new unqualified impurity; change in total impurity acceptance criteria.
3.	The change is not related to a revision of the control strategy with an intention to minimise testing of parameters and attributes (critical or non-critical).
4.	The analytical procedure remains the same.
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 specification attribute or proposal for the specific dosage form does not concern a critical attribute, for example: — identity, — assay, — purity, — impurities (except solvent is not used in the manufacture of the finished product), — critical physical characteristics (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.
8.	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 attributes.
5.	Justification/risk assessment showing that the attribute is non-significant or that it is obsolete.
6.	Justification of the new specification attribute and the acceptance criteria.

Q.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
8. Justification from the holder for the change in the testing of specification attribute. A change from routine testing to skip/periodic testing is warranted when the manufacturing process is under control and supported by a sufficient amount of historical data compliant with the specification. A change from skip/periodic testing to routine testing should be supported by analytical data demonstrating failure to meet the approved acceptance criteria for the skip tested specification.			

(*) *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' of Ph. Eur. in the dossier of an authorised medicinal finished 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.

Q.II.d.2

Q.II.d.2 **Change to analytical procedure 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 change 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, 5, 6	1	IA
(f)	To reflect compliance with the Ph. Eur. and remove reference to the outdated internal analytical procedure and analytical procedure number	2, 3, 5, 6	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.	An alternative analytical procedure is already authorised for the specification attribute.
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.

Q.II.d.2	**Change to analytical procedure for the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	6. The analytical procedure is not a biological/immunological/immunochemical procedure.			
	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.			
	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.			

Q.II.d.3

Q.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
	Introduction, replacement, or substantial change of a real-time release testing procedure			II
Note:	For changes to in-house reference standard/preparation for a biological finished product, refer to category Q.I.b.3 Change to an in-house reference standard/preparation for a biological active substance.			

Q.II.e) ***Container closure system***

Q.II.e.1

Q.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 of an approved container			
	1. Solid pharmaceutical forms	1, 2, 3, 5, 6	1, 2, 3, 5	IA
	2. Semi-solid and non-sterile liquid pharmaceutical forms		1, 2, 4, 5	IB
	3. Sterile liquid finished 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, 4, 5	IB
	2. Sterile finished products			II
(c)	Deletion of a container			
	Deletion of an immediate packaging container that does not lead to the complete deletion of a strength or pharmaceutical form	4	1, 6	IA

Q.II.e.1 **Change in immediate packaging of the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
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 finished product.			
6. The finished product is not sterile.			
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, CO_2 moisture). Where appropriate, proof must be provided that no adverse interaction between the content and the packaging material occurs (e.g. data on migration of components of the proposed material into the content and 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.			
3. 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).			
4. 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).			
5. Comparative table of the current and proposed immediate packaging specifications, if applicable.			
6. 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 Q.II.e.1.b) applicants are reminded that any change which results in a 'new pharmaceutical form' requires the submission of an Extension application.			

Q.II.e.2

Q.II.e.2	**Change in shape or dimensions of the container or closure (immediate packaging) of the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Non-sterile finished products	1, 2, 3	1, 3	IA
(b)	Sterile finished 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 one 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 at least one 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).

Q.II.e.3

Q.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

Q.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
	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.			

Q.II.e.4

Q.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 of 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, 6	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 or because of stability concerns 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.			
	6. The change is not related to a revision of the control strategy with an intention to minimise testing of parameters and attributes (critical or non-critical).			
	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.			

Q.II.e.5

Q.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 change to an approved analytical procedure	1, 2, 3	1, 2	IA
(b)	Other changes to an analytical procedure (including replacement or addition)	1, 3	1, 2	IA
(c)	Deletion of an 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 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.

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.

Q.II.e.6

Q.II.e.6	**Change in pack size of the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Introduction of a new pack size or 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 finished 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}

Q.II.e.6	**Change in pack size of the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	Conditions			
	1. New pack size should be consistent with the posology and treatment duration as approved in the summary of product characteristics.			
	2. The immediate 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 Q.II.e.6.c) and d), applicants are reminded that any changes to the 'strength' of the finished product require the submission of an Extension application.			

Q.II.e.7

Q.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, and/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 should be provided 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 relevant ISO standards, as per guideline on the *sterilisation of the medicinal product, active substance, excipient and primary container*.			

Q.II.e.8

Q.II.e.8	**Change of a secondary packaging component of the finished product (including replacement or addition or deletion), 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).			

Q.II.f) ***Stability***

Q.II.f.1

Q.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, 4	IA_{IN}
	2. After first opening	1, 6	1, 2, 3, 4	IA_{IN}
	3. After dilution or reconstitution	1, 6	1, 2, 3, 4	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 or stability modelling not in accordance with relevant stability guidelines			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

Q.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
(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 unexpected trends have been observed.			
4.	Product is not a biological or herbal finished 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 stability studies conducted in accordance with the relevant stability guidelines on three pilot scale batches (*) of the finished product in the authorised packaging material and/or two batches 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 (as annex to the application form).			
4.	Justification for the proposed change(s).			

(*) Pilot scale batches can be accepted with a commitment to verify the shelf life on production scale batches.

Q.II.g) ***Additional regulatory tools***

Q.II.g.1

Q.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 for an analytical procedure for an excipient/ intermediate and/or the finished product		1, 2, 3	IB

Q.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
(c)	Changes to, or extension of, an approved design space for the finished product and/or an analytical procedure 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).

Q.II.g.2

Q.II.g.2	**Introduction of a post-approval change management protocol related to the finished product (PACMP)**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
			1, 2, 3	II

Documentation

1.	Detailed description for the proposed change.
2.	Post-approval change management protocol related to the finished product.
3.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD).

Q.II.g.3

Q.II.g.3	**Deletion of a post-approval change management protocol (PACMP) 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 post-approval 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).

Q.II.g.4

Q.II.g.4	**Changes to a post-approval change management protocol (PACMP)**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Major changes to a post-approval change management protocol			II
(b)	Minor changes to a post-approval 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.

Q.II.g.5

Q.II.g.5	**Implementation of changes foreseen in a post-approval change management protocol (PACMP)**	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 post-approval change management protocol, which requires its notification within 12 months following implementation.
2.	The proposed change has been performed fully in line with the post-approval change management protocol, which requires its immediate notification following implementation.

Documentation

1.	Reference to the post-approval change management protocol.
2.	Declaration that the change is in accordance with the post-approval 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 post-approval 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.

Q.II.g.6

Q.II.g.6	**Introduction of a product lifecycle management document (PLCM) related to the finished 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 where relevant 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).

Q.II.g.7

Q.II.g.7	**Changes related to the finished product in line with an approved product lifecycle management document (PCLM)**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Major change to the finished product in line with an approved PLCM		1, 2, 3	II
(b)	Minor change to the finished product in line with an approved PLCM	1	1, 2, 3	IA
(c)	Minor change to the finished product in line with an approved PLCM	2	1, 2, 3	IA_{IN}
(d)	Minor change to the finished product in line with an approved PLCM		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_{IN} 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 (PLCM) with relevant sections modified.
3.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).

Q.II.g.8

Q.II.g.8	**Changes to an approved an approved product lifecycle management document (PLCM) related to the finished product**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Major changes to an approved PLCM			II
(b)	Minor changes to an approved PLCM		1, 2, 3	IB

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 (PLCM) with relevant sections modified.
3.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).

Q.II.h) ***Adventitious Agents Safety***

Q.II.h.1

Q.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 resulting in higher risk			II
	2. with modification of risk assessment resulting in equivalent or lower risk		1, 2, 3	IB
	3. without modification of risk assessment		1, 3, 4	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 modify the risk assessment resulting in equivalent or lower risk.
3.	Amendment of product information (where applicable).
4.	Justification that the studies do not modify the risk assessment.

Q.III **CEP/TSE/Monographs**

Q.III.1

Q.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) (including replacement or addition)	1, 2, 3, 4, 5, 6, 9	1, 2, 3, 4,	IA_{IN}
2.	Update of an approved certificate of suitability (CEP)	1, 2, 3, 4, 5, 9	1, 2, 3, 4,	IA
3.	Deletion of certificate(s) of suitability (CEP)	8	2	IA
4.	New certificate of suitability (CEP) for a non-sterile active substance that is to be used in a sterile finished 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 (including replacement or addition)	4, 7	1, 2, 3, 4	IA_{IN}
2.	New TSE certificate for a starting material/reagent/ intermediate/excipient (including replacement or addition)	4, 7	1, 2, 3, 4,	IA
3.	Update of an approved TSE certificate	4, 7	1, 2, 3, 4	IA
4.	Deletion of TSE certificate(s)	8	7	IA
5.	New/updated TSE certificate 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 evaluated by the holder/finished product manufacturer 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.	The holder/finished product manufacturer active substance specification for impurities is unchanged. 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.

Q.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
	3. The holder/finished product manufacturer active substance specification is unchanged for any other specific requirements that may impact finished product quality, such as polymorphism, hydration state, particle size profile.			
	4. 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.			
	5. 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.			
	6. The active substance/starting material/reagent/intermediate/excipient is not sterile.			
	7. If gelatin manufactured from bones is to be used in a finished product for parenteral use, it should only be manufactured in compliance with the relevant country requirements.			
	8. At least one manufacturer for the same substance remains in the dossier.			
	9. If the active substance is a not a sterile substance but is to be used in a sterile finished 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 holder/finished product manufacturer list of manufacturers of the active substance (Section 3.2.S.2.1). — Updated single compiled holder/finished product manufacturer active substance specification, including analytical methods and method validation (where the finished product manufacturer 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 holder/finished product manufacturer (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.			

Q.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
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).			
7.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format).			

(*) *Note:* For active substances supported by a certificate of suitability (CEP), a separate variation is required under category Q.I. 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 (Q.I.a),
— to register or amend in-house analytical procedures used by finished product manufacturer if these analytical procedures are not included on the CEP (Q.I.b),
— to register or amend a re-test period if the re-test period is not included on the CEP (Q.I.d).

Q.III.2

Q.III.2	**Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State for active substances, reagents, 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/reagent/ 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, bioassays or aggregates).

Q.III.2	**Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State for active substances, reagents, intermediates, excipients, immediate packaging materials and active substance starting materials** (*)	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	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 finished 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 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 finished product.

Q.IV **Medical devices**

Note: changes to medical devices should be submitted under the appropriate Q.IV classification, even if the medical device also acts as container closure system.

Q.IV.1

Q.IV.1	**Changes to a device 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 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 or referenced device that does not impact the delivery, quality, safety and/or efficacy of the medicinal product or the usability of the device	3, 5	1	IA

Q.IV.1	**Changes to a device co-packaged with the medicinal product or referenced in the product information**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	Conditions			
	1. The change does not have a significant impact on the delivery, quality, safety and/or efficacy of the medicinal product or the usability of the device.			
	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 of the medicinal product.			
	Documentation			
	1. Amendment of the relevant section(s) of the dossier, including description, 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.			

Q.IV.2

Q.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, 2	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 performance, safety, quality or efficacy of the medicinal product and does not contain materials of human or animal origin for which assessment is required of viral safety data or TSE risk		1, 2, 3, 4	IB

Q.IV.2	**Changes to an integral medical device (part)**	Cond. To be fulfilled	Docum. To be supplied	Proced. Type
(f)	Addition or replacement of a supplier/manufacturer of an existing device (part)	5, 6	1, 2	IA
(g)	Addition or replacement of a site responsible for sterilisation of the device (part) and/or change to the sterilisation process of the device (part) when supplied as sterile		1, 2, 5, 6	IB
(h)	Other minor change to an integral device (part)	3, 4	1, 2	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.	Justification for the absence of a Notified Body opinion/EU certificate/EU declaration of conformity, based on the risk-assessment performed, which concluded that the proposed change has no significant impact on the medicinal product.
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 O_2, CO_2 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 should be provided if it does not use the reference conditions stated in Ph. Eur..

Q.IV.3

Q.IV.3	**Changes to the dimensions, specification attributes and/or acceptance criteria 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	1	IA
(b)	Change to the specification for a medical device (part) that is not part of the final product specifications			
1.	Change to the specification acceptance criteria, 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.	Change outside 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 an analytical 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 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.

Q.IV.3	**Changes to the dimensions, specification attributes and/or acceptance criteria or analytical procedures for an integral medical device (part)**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	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:	Q.IV.3 classification applicable to specifications and analytical procedures for the medical device (part) only (3.2.P.7). Analytical procedures and specifications that are part of the final product specification and control strategy (3.2.P.5) should be classified under the appropriate Q.II category.			

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

Q.V.a) ***PMF/VAMF***

Q.V.a.1

Q.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, 5	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, 5	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 holder (where the marketing authorisation holder 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 product information whenever this is required by the relevant national legislation.			
	6. Updated affected sections of the dossier for the medicinal product.			

Q.V.a.2

Q.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 holder (where the marketing authorisation holder 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.

Q.V.b) ***Referral***

Q.V.b.1

Q.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.

C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES

General Note: In case of a change in therapeutic indication, posology or maximum daily dose, a review of quality documentation should be performed. Any resulting change to the quality documentation (for example, the need to change impurity limits) will require the submission of the appropriate quality variation under the Quality Changes chapter.

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 holder		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 holder			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. Confirmation that the proposed summary of product characteristics, labelling and package leaflet is identical for the concerned sections to that annexed to the Commission Decision or to the agreement reached by the CMDh (as applicable).
3. Revised product information.

C.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**	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 holder		1, 2, 3	IB
(b)	Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the marketing authorisation holder (e.g. comparability)			II

Documentation

1. Attached to the cover letter of the variation application: EMA/NCA request, if applicable.
2. Revised product information.

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

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 authorities.			
	2. Revised product information.			

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

C.5

C.5	**Change in the legal status of a medicinal product for centrally authorised medicinal 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

C.5	**Change in the legal status of a medicinal product for centrally authorised medicinal products**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
	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 medicinal products approved via MRP/DCP, the change of the legal status is to be handled at national level (not via a MRP variation).			

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.			

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.			

C.8

C.8	**Introduction of a summary of pharmacovigilance system for medicinal products**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
(a)	Introduction of a summary of pharmacovigilance system after a change of the holder		1, 2	IA_{IN}

Documentation

1.	Summary of the pharmacovigilance system: Proof that the holder has at its disposal a qualified person responsible for pharmacovigilance and a statement signed by the holder to the effect that it 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 to nationally authorised medicinal products.

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 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 holder 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.

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).

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.

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.

M. PMF/VAMF

M.1

M.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 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.

M.2

M.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.

M.3

M.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.

M.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
	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.			

M.4

M.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 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.			

M.5

M.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) from 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 other than administrative changes in blood establishment or centres since there were moved to non-operational (e.g. blood bags, testing kits)		1, 4, 5, 6	IB

M.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
	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 other than administrative (Type IA) changes in blood establishment or centres since they 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. Confirmation no changes other than administrative (Type IA) 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.			

M.6

M.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

M.7

M.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.			

M.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
	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.			

M.8

M.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

M.9

M.9	**Changes of an establishment or centre(s) in which storage of plasma is carried out or organisation(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 of storage establishment/centre or transport organisation		2	IB
	(c) Deletion of storage establishment/centre or transport organisation	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 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.			

M.10

M.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 (serology markers and NAT)			
	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

M.10 **Addition or replacement of blood and plasma tests**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
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			II
(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'.

M.11

M.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.

M.12

M.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, 4	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.

M.12 **Addition or replacement of blood containers (e.g. bags, bottles)**	Cond. to be fulfilled	Docum. to be supplied	Proced. type
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 Ph. Eur. requirements.			
4. Justification that there is no impact on the quality criteria of the blood in the container.			

M.13

M.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).			

M.14

M.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

M.15

M.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.			

M.16

M.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