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(Information)

INFORMATION FROM EUROPEAN UNION INSTITUTIONS, BODIES, OFFICES AND AGENCIES

EUROPEAN COMMISSION

Communication from the Commission — Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

(2010/C 17/01)

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 and veterinary medicinal products [1], hereinafter 'the variations Regulation', was published in the Official Journal on 12 December 2008. The variations Regulation aims to establish a simple, clearer and more flexible legal framework for the handling of variations to marketing authorisation of medicinal products, while ensuring a high level of protection of public and animal health.

The variations Regulation lays down general rules on the types and classification of variations in Articles 2 and 3 and in Annex II. In addition, Article 4(1)(a) charges the Commission with the task of drawing up guidelines on the details of the various categories of variations.

Consequently, this guideline provides details of the classification of variations into the following categories as defined in Article 2 of the variations Regulation: minor variations of Type IA, minor variations of Type IB and major variations of Type II and provides further details, where appropriate, on the scientific data to be submitted for specific variations and how this data should be documented. It should be noted that the general documentation accompanying every application for variations to the term of a marketing authorisation is laid down in Annex IV to the variations Regulation and in the Commission guideline on the operation of the procedures laid down in Chapters II, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.

Definitions relevant to this guideline are provided in Directive 2001/82/EC, Directive 2001/83/EC, Regulation (EC) No 726/2004 as well as in the variations Regulation. In addition, for the purpose of this guideline 'test procedure' has the same meaning as 'analytical procedure' and 'limits' have the same meaning as 'acceptance criteria'. 'Specification parameter' means the quality attribute for which a test procedure and limits are set, e.g. assay, identity and water content. The addition or deletion of a specification parameter therefore includes its corresponding test method and limits.

Where reference has to be made to specific variations in this Guideline, the variation in question should be quoted using the following structure: X.N.x.n

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

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

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

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

This guideline will be regularly updated, taking into account the recommendations delivered in accordance with Article 5 of the Regulation as well as scientific and technical progress.

[1] OJ L 334, 12.12.2008, p. 7.

2. CLASSIFICATION GUIDANCE ON MINOR VARIATIONS OF TYPE IA, MINOR VARIATIONS OF TYPE IB AND MAJOR VARIATIONS OF TYPE II

The Annex to this Guideline consists of four chapters classifying variations related to: A) Administrative changes; B) Quality changes; C) Safety, Efficacy and Pharmacovigilance changes and D) Specific changes to Plasma Master Files and Vaccine Antigen Master Files.

For each chapter the Annex contains:

— a list of variations which should be classified as minor variations of Type IA or major variations of Type II in accordance with the definitions of Article 2 of the variations Regulation and the classifications provided in Annex II to the variations Regulation. It is also indicated which minor variations of Type IA require immediate notification as established in Article 8(1) of the variations Regulation,

— a list of examples that should be considered as minor variations of Type IB, in the understanding that this category applies by default as established in Article 3 of the variations Regulation and that the Annex to this Guideline does not therefore attempt to establish an exhaustive list for this category of variations.

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

When one or more of the conditions established in the Annex to this Guideline for a minor variation of Type IA are not met, the concerned change may be submitted as a Type IB variation unless the change is specifically classified as a major variation of Type II.

Specific supporting data for Type IB and Type II variations will depend on the specific nature of the change. In some cases, reference is made to specific scientific guidelines.

Furthermore, if a variation leads to a revision of the summary of product characteristics, labelling or package leaflet (in this guideline jointly referred to as 'the product information'), this change is considered part of that variation. In such cases updated product information has to be submitted as part of the application. Mock-ups or specimens should be provided according to 'The rules governing medicinal products in the European Community', Volume 2A, Procedures for marketing authorisations; Chapter 7, General information of the Notice to applicants (hereinafter Chapter 7 of Notice to applicants), or as discussed with the reference Member State or the Agency on a case-by-case basis.

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 compliance with the updated monograph is implemented within six months of its publication and reference is made to the 'current edition' in the dossier of an authorised medicinal product.

Any change to the content of the dossier that supports a European Pharmacopoeia Certificate of Suitability, should be submitted to the European Directorate for the Quality of Medicines (EDQM). However, if the certificate is revised following EDQM evaluation of this change, any marketing authorisation concerned must be updated accordingly.

With reference to Part III point 1 of Annex I to Directive 2001/83/EC, changes to Plasma Master Files (hereinafter PMFs) and Vaccine Antigen Master Files (VAMFs) follow the evaluation procedures for variations set-out in the variations Regulation. Therefore, Chapter D in this guideline provides a list of variations which are specific to such PMFs or VAMFs. Following review of these variations, any marketing authorisation concerned must be updated in accordance with Chapter B.V of this guideline. In case the documentation of the human plasma used as starting material for a plasma derived medicinal product is not submitted as a PMF, variations to this starting material as described in the marketing authorisation dossier should also be handled in accordance with this Annex.

References in this guideline to changes to the marketing authorisation dossier mean addition, replacement or deletion, unless specifically indicated. If amendments to the dossier only concern editorial changes, such changes should generally not be submitted as a separate variation, but they can be included in a variation concerning that part of the dossier. In such cases a declaration that the content of the concerned part of the dossier has not been changed by the editorial changes beyond the substance of the variation submitted should be provided.

ANNEX

A. **ADMINISTRATIVE CHANGES**

A.1 Change in the name and/or address of the marketing authorisation holder	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	**1, 2**	**IA_{IN}**

Conditions

1. The marketing authorisation holder shall remain the same legal entity.

Documentation

1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.
2. Revised product information.

A.2 Change in the (invented) name of the medicinal product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) for Centrally Authorised products	**1**	**1, 2**	**IA_{IN}**
b) for Nationally Authorised Products		**2**	**IB**

Conditions

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

Documentation

1. Copy of the EMEA letter of acceptance of the new (invented) name.
2. Revised product information.

A.3 Change in name of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1, 2	**1, 2**	**IA_{IN}**

Conditions

1. The active substance shall remain the same.
2. For veterinary medicinal products for food-producing species, the new name has been published in Regulation (EC) No 470/2009 before implementation of this change.

Documentation

1. Proof of acceptance by WHO or copy of the INN list. For herbal medicinal product, declaration that the name is in accordance with the Note for Guidance on Quality of Herbal Medicinal Products, and with the guideline on declaration of herbal substances and herbal preparations in (traditional) herbal medicinal products.
2. Revised product information

A.4 Change in the name and/or address of a manufacturer (including where relevant quality control sites) or supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the product dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	**1, 2, 3**	**IA**

Conditions

1. The manufacturing site and all manufacturing operations shall remain the same.

Documentation

1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name and/or address is mentioned.
2. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
3. In case of change in the name of the holder of the Active Substance Master File holder, updated 'letter of access'.

A.5 Change in the name and/or address of a manufacturer of the finished product, including quality control sites	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Manufacturer responsible for batch release	**1**	**1, 2**	**IA_{IN}**

b) All other	**1**	**1, 2**	**IA**

Conditions

1. The manufacturing site and all manufacturing operations shall remain the same.

Documentation

1. Copy of the modified manufacturing authorisation, if available; or a formal document from a relevant official body (e.g. Chamber of Commerce, or if not available, from a Regulatory Agency) in which the new name and/or address is mentioned.
2. If applicable, amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.

A.6 Change in ATC Code/ATC Vet Code	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	**1, 2**	**IA**

Conditions

1. Change following granting of or amendment to ATC Code by WHO/ATC Vet Code.

Documentation

1. Proof of acceptance (by WHO) or copy of the ATC (Vet) Code list.
2. Revised product information

A.7 Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1, 2	**1, 2**	**IA**

Conditions

1. There should at least remain one site/manufacturer, as previously authorised, performing the same function as the one(s) concerned by the deletion.
2. The deletion should not be due to critical deficiencies concerning manufacturing.

Documentation

1. The variation application form should clearly outline the 'present' and 'proposed' manufacturers as listed in section 2.5 of the (Part IA) application form.
2. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.

B. **QUALITY CHANGES**

B.I ACTIVE SUBSTANCE

B.I.a) *Manufacture*

B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer.	**1, 2, 3**	**1, 2, 3, 4, 5, 6, 7**	**IA_{IN}**
b) Introduction of a new manufacturer of the active substance that is supported by an ASMF			**II**

c) The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability.			**II**
d) New manufacturer of material for which an assessment is required of viral safety and/or TSE risk			**II**
e) The change relates to a biological active substance or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product.			**II**
f) Changes to quality control testing arrangements for the active substance-replacement or addition of a site where batch control/testing takes place	**2, 4**	**1, 5**	**IA**

Conditions

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

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

3. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.*

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

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), if applicable.

2. A declaration from the marketing authorisation holder or the ASMF holder, where applicable, that the synthetic route (or in case of herbal medicinal products, where appropriate the method of preparation, geographical source, production of herbal drug and manufacturing route) quality control procedures and specifications of the active substance and of the starting material/reagent/intermediate in the manufacturing process of the active substance (if applicable) are the same as those already approved.

3. Either a TSE Ph. Eur. Certificate of Suitability for any new source of material or, where applicable, documentary evidence that the specific source of the TSE risk material has previously been assessed by the 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) of the active substance from the current and proposed manufacturers/sites.

5. The variation application form should clearly outline the 'present' and 'proposed' manufacturers as listed in section 2.5 of the (Part IA) application form.

6. A declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances - see the note under variation no. B.II.b.1

7. Where relevant, a commitment of the manufacturer of the active substance to inform the MA holder of any changes to the manufacturing process, specifications and test procedures of the active substance

B.I.a.2 Changes in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor change in the manufacturing process of the active substance	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 3**	**IA**
b) Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the medicinal product.			**II**
c) The change refers to a biological/immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol.			**II**
d) The change relates to a herbal medicinal product and there is a change to any of the following: geographical source, manufacturing route or production.			**II**
e) Minor change to the restricted part of an Active Substance Master File.		**1, 2, 3, 4**	**IB**

Conditions

1. No adverse change in qualitative and quantitative impurity profile or in physico-chemical properties.
2. The synthetic route remains the same, i.e. intermediates remain the same and there are no new reagents, catalysts or solvents used in the process. In the case of herbal medicinal products, the geographical source, production of the herbal substance and the manufacturing route remain the same.
3. The specifications of the active substance or intermediates are unchanged.
4. The change is fully described in the open ('applicant's') part of an Active Substance Master File, if applicable.
5. The active substance is not a biological/immunological substance.
6. The change does not refer to the geographical source, manufacturing route or production of a herbal medicinal product.
7. The change does not refer to the restricted part of an Active Substance Master File.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), and of the approved Active Substance Master File (where applicable), including a direct comparison of the present process and the new process.
2. Batch analysis data (in comparative tabular format) of at least two batches (minimum pilot scale) manufactured according to the currently approved and proposed process.
3. Copy of approved specifications of the active substance.
4. A declaration from the marketing authorisation holder or the ASMF Holder, where applicable, that there is no change in qualitative and quantitative impurity profile or in physico-chemical properties, that the synthetic route remains the same and that the specifications of the active substance or intermediates are unchanged.

Note: For B.I.a.2.b For chemical active substances, this refers to substantial changes to the synthetic route or manufacturing conditions which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability.

B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Up to 10-fold increase compared to the currently approved batch size	**1, 2, 3, 4, 6, 7, 8**	**1, 2, 5**	**IA**
b) Downscaling	**1, 2, 3, 4, 5**	**1, 2, 5**	**IA**
c) The change requires assessment of the comparability of a biological/immunological active substance.			**II**
d) More than 10-fold increase compared to the currently approved batch size		**1, 2, 3, 4**	**IB**

e) The scale for a biological/immunological active substance is increased/decreased without process change (e.g. duplication of line).		**1, 2, 3, 4**	**IB**

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 product concerned is not a biological/immunological medicinal product.
4. The change does not adversely affect the reproducibility of the process.
5. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.
6. The specifications of the active substance/intermediates remain the same.
7. The active substance is not sterile.
8. The currently approved batch size was not approved via a Type IA variation.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
2. The batch numbers of the tested batches having the proposed batch size.
3. Batch analysis data (in a comparative tabulated format) on a minimum of one production batch of the active substance or intermediate as appropriate, manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).
4. Copy of approved specifications of the active substance (and of the intermediate, if applicable).
5 A declaration from the marketing authorisation holder or the ASMF holder as appropriate that the changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during manufacture or because of stability concerns and that the specifications of the active substance/intermediates remain the same.

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

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way
6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods)

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
2. Comparative table of current and proposed in-process tests.
3. Details of any new non-pharmacopoeial analytical method and validation data, where relevant.
4. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the active substance for all specification parameters.
5. Justification/risk-assessment from the marketing authorisation holder or the ASMF Holder as appropriate showing that the parameter is non-significant.
6. Justification from the MAH or ASMF Holder as appropriate for the new in-process test and limits.

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

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

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

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.

3. Any change should be within the range of currently approved limits.

4. The test procedure remains the same, or changes in the test procedure are minor.

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

6. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeia microbiological methods).

7. The change does not concern a genotoxic impurity.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Comparative table of current and proposed specifications.

3. Details of any new analytical method and validation data, where relevant.

4. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the relevant substance for all specification parameters.

5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.

6. Justification/risk-assessment from the MAH or ASMF holder as appropriate showing that the parameter is non-significant.

7. Justification from the MAH or ASMF Holder as appropriate of the new specification parameter and the limits.

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

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.

2. There have been no changes of the total impurity limits; no new unqualified impurities are detected.

3. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).

4. The test method is not a biological/immunological/immunochemical method, or a method using a biological reagent for a biological active substance. (does not include standard pharmacopoeial microbiological methods).

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

6. The active substance is not biological/immunological.

7. An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA(IN) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).
2. Comparative validation results, or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.I.c) *Container closure system*

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

Conditions

1. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.
2. Relevant stability studies have been started under ICH conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging, the three months' stability data do not yet have to be available. These studies must be finalised and the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the shelf-life/retest period (with proposed action).
3. Sterile, liquid and biological/immunological active substances are excluded.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
2. Appropriate data on the new packaging (e.g. comparative data on permeability e.g. for O_2, CO_2 moisture), including a confirmation that the material complies with relevant pharmacopoeial requirements or legislation of the Union on plastic materials and objects in contact with foodstuffs.
3. Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeia requirements or legislation of the Union on plastic material and objects in contact with foodstuffs.
4. A declaration from the marketing authorisation holder or the ASMF holder as appropriate that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
5. The results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of three months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved retest period (with proposed action).
6. Comparison of the current and proposed immediate packaging specifications, if applicable.

B.I.c.2 Change in the specification parameters and/or limits of the immediate packaging of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5**	**1, 2, 3, 4, 6**	**IA**

c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**1, 2**	**1, 2, 5**	**IA**
d) Addition or replacement of a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4, 6**	**IB**

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure) unless it has been previously assessed and agreed as part of a follow-up measure.

2. The change does not result from unexpected events arising during manufacture of the packaging material or during storage of the active substance.

3. Any change should be within the range of currently approved limits.

4. The test procedure remains the same, or changes in the test procedure are minor.

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Comparative table of current and proposed specifications.

3. Details of any new analytical method and validation data, where relevant.

4. Batch analysis data on two batches of the immediate packaging for all specification parameters.

5 Justification/risk-assessment from the marketing authorisation holder or the ASMF Holder, as appropriate, showing that the parameter is non-significant.

6. Justification from the marketing authorisation holder or the ASMF Holder, as appropriate, of the new specification parameter and the limits.

B.I.c.3 Change in test procedure for the immediate packaging of the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor changes to an approved test procedure	**1, 2, 3,**	**1, 2**	**IA**
b) Other changes to a test procedure (including replacement or addition)	**1, 3, 4**	**1, 2**	**IA**
c) Deletion of a test procedure if an alternative test procedure is already authorised	**5**	**1**	**IA**

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.

2. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).

3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

4. The active substance/finished product is not biological/immunological.

5. There is still a test procedure registered for the specification parameter and this procedure has not been added through a IA/IA(IN) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a description of the analytical methodology, a summary of validation data.

2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.I.d) *Stability*

B.I.d.1 Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Re-test period/storage period			
1. Reduction	**1**	**1, 2, 3**	**IA**
2. Extension of the retest period based on extrapolation of stability data not in accordance with ICH guidelines (*)			**II**
3. Extension of storage period of a biological/immunological active substance not in accordance with an approved stability protocol.			**II**
4. Extension or introduction of a re-test period/storage period supported by real time data		**1, 2, 3**	**IB**
b) Storage conditions			
1. Change to more restrictive storage conditions of the active substance	**1**	**1, 2, 3**	**IA**
2. Change in storage conditions of biological/immunological active substances, when the stability studies have not been performed in accordance with a currently approved stability protocol			**II**
3. Change in storage conditions of the active substance		**1, 2, 3**	**IB**

Conditions

1. 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 or NTA volume 6B format for veterinary products, as appropriate). This must contain results of appropriate real time stability studies, conducted in accordance with the relevant stability guidelines on at least two (three for biological medicinal products) pilot or production scale batches of the active substance in the authorised packaging material and covering the duration of the requested re-test period or requested storage conditions.
2. Confirmation that stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.
3. Copy of approved specifications of the active substance.

(*) *Note:* retest period not applicable for biological/immunological active substance.

B.I.e) *Design Space*

B.I.e.1 Introduction of a new design space or extension of an approved design space for the active substance, concerning	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) One unit operation in the manufacturing process of the active substance including the resulting in-process controls and/or test procedures		1, 2, 3	II
b) Test procedures for starting materials/reagents/intermediates and/or the active substance		1, 2, 3	II

Documentation

1. The design space has been developed in accordance with the relevant European and international scientific guidelines. Results from product, process and analytical development studies (e.g. interaction of the different parameters forming the design space have to be studied, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the active substance has been achieved.
2. Description of the Design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.
3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

B.I.e.2 Introduction of a post approval change management protocol related to the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
		1, 2	**II**

Documentation

1. Detailed description for the proposed change.
2. Change management protocol related to the active substance.

B.I.e.3 Deletion of an approved change management protocol related to the active substance	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	**1**	**IA_{IN}**

Conditions

1. The deletion of the approved change management protocol related to the active substance is not a result of unexpected events or out of specification results during the implementation of the change (s) described in the protocol.

Documentation

1. Justification for the proposed deletion.

B.II FINISHED PRODUCT

B.II.a) *Description and composition*

B.II.a.1 Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Changes in imprints, bossing or other markings	**1, 2, 3**	**1, 2**	**IA_{IN}**
b) Changes in scoring/break lines intended to divide into equal doses		**1, 2, 3**	**IB**

Conditions

1. Finished product release and end of shelf life specifications have not been changed (except for appearance).
2. Any ink must comply with the relevant pharmaceutical legislation.
3. The scoring/break lines are not intended to divide into equal doses.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a detailed drawing or written description of the current and new appearance, and including revised product information as appropriate.
2. Samples of the finished product where applicable (see NTA, Requirements for samples in the Member States).
3. Results of the appropriate Ph. Eur tests demonstrating equivalence in characteristics/correct dosing.

B.II.a.2 Change in the shape or dimensions of the pharmaceutical form	Conditions to be fulfilled	Documentation to be supplied	Procedure 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, 5**	**IB**

Conditions

1. If appropriate, the dissolution profile of the reformulated product is comparable to the old one. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the new product compared to the old one.

2. Release and end of shelf-life specifications of the product have not been changed (except for dimensions).

3. The qualitative or quantitative composition and mean mass remain unchanged.

4. The change does not relate to a scored tablet that is intended to be divided into equal doses.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), 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 (Human or Veterinary) guidance on Bioavailability). For herbal medicinal product comparative disintegration data may be acceptable.

3. Justification for not submitting a new bioequivalence study according to the relevant (Human or Veterinary) guidance on Bioavailability.

4. Samples of the finished product where applicable (see NTA, Requirements for samples in the Member States).

5. Results of the appropriate Ph. Eur tests demonstrating equivalence in characteristics/correct dosing.

B.II.a.3 Changes in the composition (excipients) of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Changes 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, 6**	**IA_{IN}**
2. Increase or reduction	**1, 2, 3, 4**	**1, 2, 4**	**IA**
3. Biological veterinary medicinal products for oral use for which the colouring or flavouring agent is important for the uptake by target animal species			**II**
b) Other excipients			
1. Any minor adjustment of the quantitative composition of the finished product with respect to excipients	**1, 2, 4, 8, 9, 10**	**1, 2, 7**	**IA**
2. Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the medicinal product.			**II**
3. Change that relates to a biological/immunological product			**II**
4. Any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk.			**II**

5. Change that is supported by a bioequivalence study.			**II**
6. Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level		**1, 3, 4, 5, 6, 7, 8, 9, 10**	**IB**

Conditions

1. No change in functional characteristics of the pharmaceutical form e.g. disintegration time, dissolution profile.

2. Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the finished product formulation.

3. The finished product specification has only been updated in respect of appearance/odour/taste and if relevant, deletion of an identification test.

4. Stability studies have been started under ICH conditions (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant (at time of implementation for Type IAs and at time of notification for Type IBs) and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specification at the end of the approved shelf life (with proposed action). In addition, where relevant, photo-stability testing should be performed.

5. Any new proposed components must comply with the relevant Directives (e.g. Directive 94/36/EC and 2008/128/EC for colours for use in foodstuffs and Directive 88/388/EEC 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 (Human or Veterinary) guidance on Bioavailability). 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/immunological medicinal product.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including identification method for any new colorant, where relevant, and including revised product information as appropriate.

2. A declaration that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the 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 three months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

4. Sample of the new product, where applicable (see Notice to Applicants Requirements for samples in the Member States).

5. Either a Ph. Eur. Certificate of Suitability for any new component of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by the competent authority and shown to comply with the scope of the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products*. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.

   For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).

6. Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate.

7. Justification for the change/choice of excipients etc. must be given by appropriate development pharmaceutics (including stability aspects and antimicrobial preservation where appropriate).

8. For solid dosage forms, comparative dissolution profile data of at least two pilot scale batches of the finished product in the new and old composition. For herbal medicinal products, comparative disintegration data may be acceptable.

9. Justification for not submitting a new bioequivalence study according to the current *Note for Guidance on The Investigation of Bioavailability and Bioequivalence*.

10. For veterinary medicines intended for use in food producing animal species, proof that the excipient is classified according to Article 14(2)(c) of Regulation (EC) No 470/2009 of the European Parliament and the Council of 6 May 2009 laying down Community procedures for the establishment of residue limits of pharmacologically active substances in foodstuffs of animal origin, repealing Council Regulation (EEC) No 2377/90 and amending Directive 2001/82/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council or, if not, justification that the excipient does not have pharmacological activity at the dose at which it is administered to the target animal.

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

Conditions

1. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one. For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.

2. The coating is not a critical factor for the release mechanism.

3. The finished product specification has only been updated in respect of weight and dimensions, if applicable.

4. Stability studies in accordance with the relevant guidelines have been started with at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant at the time of implementation and assurance that these studies will be finalised. Data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, 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). In addition, where relevant, photo-stability testing should be performed.

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

B.II.a.6 Deletion of the solvent/diluent container from the pack	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
		1, 2	**IB**

Documentation

1. Justification for the deletion, including a statement regarding alternative means to obtain the solvent/diluent as required for the safe and effective use of the medicinal product.

2. Revised product information

B.II.b) *Manufacture*

B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Secondary packaging site	**1, 2**	**1, 3, 8**	**IA_{IN}**
b) Primary packaging site	**1, 2, 3, 4, 5**	**1, 2, 3, 4, 8, 9**	**IA_{IN}**
c) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products.			**II**
d) Site which requires an initial or product specific inspection			**II**
e) Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products.		**1, 2, 3, 4, 5, 6, 7, 8, 9**	**IB**
f) Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products manufactured using an aseptic method excluding biological/immunological medicinal products.		**1, 2, 3, 4, 5, 7, 8**	**IB**

Conditions

1. Satisfactory inspection in the last three years by an inspection service of one of the Member States of the EEA or of a country where an operational Good Manufacturing Practice (GMP) mutual recognition agreement (MRA) exists between the country concerned and the EU.

2. Site appropriately authorised (to manufacture the pharmaceutical form or product concerned).

3. Product concerned is not a sterile product.

4. Where relevant, for instance for suspensions and emulsions, validation scheme is available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches.

5. Product concerned is not a biological/immunological medicinal product.

Documentation

1. Proof that the proposed site is appropriately authorised for the pharmaceutical form or product concerned, i.e.:

   For a manufacturing site within the EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMP database will suffice once the public version is operational;

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

   For a manufacturing site outside the EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EEA. A reference to the EudraGMP database will suffice once the public version is operational.

2. Where relevant, the batch numbers, corresponding batch size and the manufacturing date of batches (33) used in the validation study should be indicated and the validation data presented, or validation protocol (scheme) to be submitted.

3. The variation application form should clearly outline the 'present' and 'proposed' finished product manufacturers as listed in section 2.5 of the (Part IA) application form.

4. Copy of approved release and end-of-shelf life specifications if relevant.

5. Batch analysis data on one production batch and two pilot-scale batches simulating the production process (or two production batches) and comparative data on the last three batches from the previous site; batch data on the next two production batches should be available on request or reported if outside specifications (with proposed action).

6. For semisolid and liquid formulations in which the active substance is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology.

7. i) If the new manufacturing site uses the active substance as a starting material – A declaration by the Qualified Person (QP) at the site responsible for batch release that the active substance is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union.

   ii) In addition, if the new manufacturing site is located within the EEA and uses the active substance as a starting material – A declaration by the Qualified Person (QP) of the new manufacturing site that the active substance used is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union.

8. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

9. If the manufacturing site and the primary packaging site are different, conditions of transport and bulk storage should be specified and validated

Notes: In case of a change in or a new manufacturing site in a country outside the 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 EEA inspection in the last 2-3 years and/or any planned EEA inspection(s) including inspection dates, product category inspected, Supervisory Authority and other relevant information. This will facilitate the arrangement for a GMP inspection by an inspection service of one of the Member States if needed.

QP Declarations in relation to active substances

Manufacturing authorisation holders are obliged to only use as starting materials active substances that have been manufactured in accordance with GMP so a declaration is expected from each of the manufacturing authorisation holders that use the active substance as a starting material. In addition, as the QP responsible for batch certification takes overall responsibility for each batch, a further declaration from the QP responsible for batch certification is expected when the batch release site is a different site from the above.

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

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

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

Applicants are reminded that a Qualified Person is at the disposal of a manufacturing authorisation holder according to Art. 41 of Directive 2001/83/EC and Article 45 of Directive 2001/82/EC and located in the EEA. Therefore declarations from personnel employed by manufacturers in third countries, including those located within MRA partner countries are not acceptable.

According to Article 46a (1) of Directive 2001/83/EC and Article 50a (1) of Directive 2001/82/EC, manufacture includes complete or partial manufacture, import, dividing up, packaging or presentation prior to its incorporation into a medicinal product, including re-packaging or re-labelling as carried out by a distributor.

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

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

Conditions

1. The manufacturer responsible for batch release must be located within the EEA.

2. The site is appropriately authorised.

3. The product is not a biological/immunological medicinal product.

4. Method transfer from the old to the new site or new test laboratory has been successfully completed.

Documentation

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

   For a manufacturing site outside the EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate, issued within the last 3 years by the relevant competent authority. Where no such agreement exists a GMP certificate issued within the last 3 years by a EU/EEA competent authority.

2. The variation application form should clearly outline the 'present' and 'proposed' finished product manufacturers as listed in section 2.5 of the (Part IA) application form.

3. For centralised procedure only: contact details of new contact person in the EEA for product defects and recalls, if applicable.

4. A declaration by the Qualified Person (QP) responsible for batch certification stating that the active substance manufacturer(s) referred to in the marketing authorisation operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances - see the note under variation no B.II.b.1

5 Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.

B.II.b.3 Change in the manufacturing process of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions.	**1, 2, 3, 4, 5, 6, 7**	**1, 3, 4, 6, 7, 8**	**IA**
b) Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product			**II**
c) The product is a biological/immunological medicinal product and the change requires an assessment of comparability.			**II**
d) Introduction of a non-standard terminal sterilisation method			**II**
e) Introduction or increase in the overage that is used for the active substance			**II**
f) Minor change in the manufacturing process of an aqueous oral suspension.		**1, 2, 4, 6, 7, 8**	**IB**

Conditions

1. No change in qualitative and quantitative impurity profile or in physico-chemical properties.

2. The product concerned is not a biological/immunological or herbal medicinal product.

3. The manufacturing principle including the single manufacturing steps remain the same, e.g. processing intermediates and there are no changes to any manufacturing solvent used in the process.

4 The currently registered process has to be controlled by relevant in-process controls and no changes (widening or deletion of limits) are required to these controls.

5. The specifications of the finished product or intermediates are unchanged.

6. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.

7. Relevant stability studies in accordance with the relevant guidelines have been started with at least one pilot scale or industrial scale batch and at least three months stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), 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 (Human or Veterinary) guidance on Bioavailability.

5. In case of a change to the sterilisation process, validation data should be provided.

6. Copy of approved release and end-of-shelf life specifications.

7. Batch analysis data (in a comparative tabulated format) on a minimum of one batch manufactured to both the currently approved and the proposed process. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).

8. Declaration that relevant stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and relevant stability parameters have been assessed in at least one pilot scale or industrial scale batch and at least three months satisfactory stability data are at the disposal of the applicant at time of notification and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

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

Conditions

1. The change does not affect reproducibility and/or consistency of the product.

2. The change relates to standard immediate release oral pharmaceutical forms or to non-sterile liquid based pharmaceutical forms.

3. Any changes to the manufacturing method and/or to the in-process controls are only those necessitated by the change in batch-size, e.g. use of different sized equipment.

4. Validation scheme is available or validation of the manufacture has been successfully carried out according to the current protocol with at least three batches at the proposed new batch size in accordance with the relevant guidelines.

5. The product concerned is not a biological/immunological medicinal product.

6. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.

7. The currently approved batch size was not approved via a Type IA variation.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Batch analysis data (in a comparative tabulated format) on a minimum of one production batch manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the MAH if outside specifications (with proposed action).

3. Copy of approved release and end-of-shelf life specifications.

4. Where relevant the batch numbers, corresponding batch size and the manufacturing date of batches (≥ 3) used in the validation study should be indicated or validation protocol (scheme) be submitted.

5. The validation results should be provided.

6. The results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least one pilot or industrial scale batch, covering a minimum period of three months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). For biologicals/immunologicals: a declaration that an assessment of comparability is not required.

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

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).

2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.

3. Any change should be within the range of currently approved limits.

4. The test procedure remains the same, or changes in the test procedure are minor.

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Comparative table of current and proposed in-process tests and limits.

3. Details of any new analytical method and validation data, where relevant.

4. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters.

5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch manufactured using the current and new in-process tests. For herbal medicinal products, comparative disintegration data may be acceptable.

6 Justification/risk-assessment showing that the parameter is non-significant.

7. Justification of the new in-process test and limits.

B.II.c) *Control of excipients*

B.II.c.1 Change in the specification parameters and/or limits of an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 6, 8**	**IA**
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**1, 2**	**1, 2, 7**	**IA**
d) Change outside the approved specifications limits range			**II**
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product			**II**
f) Addition or replacement (excluding biological or immunological product) of a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4, 5, 6, 8**	**IB**

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The test method is not a biological/immunological/immunochemical method, or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).
7. The change does not concern a genotoxic impurity.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
2. Comparative table of current and proposed specifications.
3. Details of any new analytical method and validation data, where relevant.
4. Batch analysis data on two production batches (3 production batches for biological excipients) of the excipient for all specification parameters.
5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the excipient complying with the current and proposed specification. For herbal medicinal products comparative disintegration data may be acceptable.
6. Justification for not submitting a new bioequivalence study according to the relevant (Human, Veterinary) Guideline on *Bioavailability*, if appropriate.
7. Justification/risk-assessment showing that the parameter is non-significant.
8. Justification of the new specification parameter and the limits.

B.II.c.2 Change in test procedure for an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor changes to an approved test procedure	**1, 2, 3, 4**	**1, 2**	**IA**
b) Deletion of a test procedure if an alternative test procedure is already authorised	**5**	**1**	**IA**
c) Replacement of a biological/immunological/immunochemical test method or a method using a biological reagent			**II**

d) Other changes to a test procedure (including replacement or addition)		**1, 2**	**IB**

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.

2. There have been no changes of the total impurity limits; no new unqualified impurities are detected.

3. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).

4. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).

5. An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA(IN) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).

2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

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

Conditions

1. Excipient and finished product release and end of shelf life specifications remain the same.

Documentation

1. Declaration from the manufacturer or the marketing authorisation holder of the material that it is purely of vegetable or synthetic origin.

2. Study of equivalence of the materials and the impact on production of the final material and impact on behaviour (e.g. Dissolution characteristics) of the finished product.

B.II.c.4 Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor change in synthesis or recovery of a non-pharmacopoeial excipient	**1, 2**	**1, 2, 3, 4**	**IA**
b) The specifications are affected or there is a change in physico-chemical properties of the excipient which may affect the quality of the finished product.			**II**
c) The excipient is a biological/immunological substance			**II**

Conditions

1. The synthetic route and specifications are identical and there is no change in qualitative and quantitative impurity profile (excluding residual solvents, provided they are controlled in accordance with (V)ICH limits), or in physico-chemical properties.
2. Adjuvants are excluded.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
2. Batch analysis data (in a comparative tabulated format) of at least two batches (minimum pilot scale) of the excipient manufactured according to the old and the new process.
3. Where appropriate, comparative dissolution profile data for the finished product of at least two batches (minimum pilot scale). For herbal medicinal products, comparative disintegration data may be acceptable.
4. Copy of approved and new (if applicable) specifications of the excipient.

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

B.II.d.1 Change in the specification parameters and/or limits of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Tightening of specification limits for medicinal products subject to Official Batch Release	**1, 2, 3, 4**	**1, 2**	**IA_{IN}**
c) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 7**	**IA**
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter	**1, 2**	**1, 2, 6**	**IA**
e) Change outside the approved specifications limits range			**II**
f) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product			**II**
g) Addition or replacement (excluding biological or immunological product) of a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4, 5, 7**	**IB**

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way
6. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance
7. The change does not concern a genotoxic impurity.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
2. Comparative table of current and proposed specifications.
3. Details of any new analytical method and validation data, where relevant.

4. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters.

5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.

6 Justification/risk-assessment showing that the parameter is non-significant.

7. Justification of the new specification parameter and the limits.

B.II.d.2 Change in test procedure for the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor changes to an approved test procedure	**1, 2, 3, 4**	**1,2**	**IA**
b) Deletion of a test procedure if an alternative method is already authorised	**4**	**1**	**IA**
c) Replacement of a biological/immunological/immunochemical test method or a method using a biological reagent.			**II**
d) Other changes to a test procedure (including replacement or addition)		**1, 2**	**IB**

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.

2. There have been no changes of the total impurity limits; no new unqualified impurities are detected.

3. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).

4. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).

2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent.; This requirement is not applicable in case of an addition of a new test procedure.

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

Documentation

B.II.e) *Container closure system*

B.II.e.1 Change in immediate packaging of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Qualitative and quantitative composition			
1. Solid pharmaceutical forms	**1, 2, 3**	**1, 2, 3, 4, 6**	**IA**
2. Semi-solid and non-sterile liquid pharmaceutical forms		**1, 2, 3, 5, 6**	**IB**
3. Sterile medicinal products and biological/immunological medicinal products.			**II**
4. The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.			**II**

b) Type of container			
1. Solid, semi-solid and non-sterile liquid pharmaceutical forms		**1, 2, 3, 5, 6, 7**	**IB**
2. Sterile medicinal products and biological/immunological medicinal products			**II**

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).

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.
2. Appropriate data on the new packaging (comparative data on permeability e.g. for O_2, CO_2 moisture).
3. Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeial requirements or legislation of the Union on plastic material and objects in contact with foodstuffs.
4. A declaration that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
5. The results of stability studies that have been carried out under ICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of three months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
6. Comparative table of the current and proposed immediate packaging specifications, if applicable.
7. Samples of the new container/closure where applicable (see NTA, Requirements for samples in the Member States/EMEA).

Note: For B.II.e.1.b) applicants are reminded that any change which results in a 'new pharmaceutical form' requires the submission of an Extension application.

B.II.e.2 Change in the specification parameters and/or limits of the immediate packaging of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5**	**1, 2, 3, 4, 6**	**IA**
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**1, 2**	**1, 2, 5**	**IA**
d) Addition or replacement of a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4, 6**	**IB**

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes in the test procedure are minor.

5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
2. Comparative table of current and proposed specifications.
3. Details of any new analytical method and validation data, where relevant.
4. Batch analysis data on two batches of the immediate packaging for all specification parameters.
5. Justification/risk-assessment showing that the parameter is non-significant.
6. Justification of the new specification parameter and the limits.

B.II.e.3 Change in test procedure for the immediate packaging of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Minor changes to an approved test procedure	**1, 2, 3**	**1, 2**	**IA**
b) Other changes to a test procedure (including replacement or addition)	**1, 3, 4**	**1, 2**	**IA**
c) Deletion of a test procedure if an alternative test procedure is already authorised	**5**	**1**	**IA**

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and validation studies show that the updated test procedure is at least equivalent to the former test procedure.
2. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
4. The active substance/finished product is not biological/immunological.
5. An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA(IN) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a description of the analytical methodology, a summary of validation data.
2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Non-sterile medicinal products	**1, 2, 3**	**1, 2, 4**	**IA**
b) The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product			**II**
c) Sterile medicinal products		**1, 2, 3, 4**	**IB**

Conditions

1. No change in the qualitative or quantitative composition of the container.
2. The change does not concern a fundamental part of the packaging material, which affects the delivery, use, safety or stability of the finished product.
3. In case of a change in the headspace or a change in the surface/volume ratio, stability studies in accordance with the relevant guidelines have been started and relevant stability parameters have been assessed in at least two pilot scale (three for biological/immunological medicinal products) or industrial scale batches and at least three months (six months for biological/immunological medicinal products) stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that data will be provided immediately to the 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 or NTA volume 6B format for veterinary products, as appropriate), including description, detailed drawing and composition of the container or closure material, and including revised product information as appropriate.

2. Samples of the new container/closure where applicable (see NTA, Requirements for samples in the Member States).

3. Re-validation studies have been performed in case of sterile products terminally sterilised. The batch numbers of the batches used in the re-validation studies should be indicated, where applicable.

4. In case of a change in the headspace or a change in the surface/volume ratio, a declaration that the required stability studies have been started under ICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation for a Type IA notification and time of submission of a Type IB notification, and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).

B.II.e.5 Change in pack size of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Change in the number of units (e.g. tablets, ampoules, etc.) in a pack			
1. Change within the range of the currently approved pack sizes	**1, 2**	**1, 3**	**IA_{IN}**
2. Change outside the range of the currently approved pack sizes		**1, 2, 3**	**IB**
b) Deletion of a pack size(s)	**3**	**1, 2**	**IA**
c) Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, and biological/immunological multidose parenteral medicinal products.			**II**
d) Change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) products		**1, 2, 3**	**IB**

Conditions

1. New pack size should be consistent with the posology and treatment duration as approved in the Summary of Product Characteristics.

2. The primary packaging material remains the same.

3. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the Summary of Product Characteristics.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate) 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 use as approved in the summary of product characteristics

3. Declaration that stability studies will be conducted in accordance with the relevant guidelines for products where stability parameters could be affected. Data to be reported only if outside specifications (with proposed action).

Note: For B.II.e.5.c) and d), applicants are reminded that any changes to the 'strength' of the medicinal product require the submission of an Extension application.

B.II.e.6 Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used))	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Change that affects the product information	**1**	**1**	**IA_{IN}**
b) Change that does not affect the product information	**1**	**1**	**IA**

Conditions

1. The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.

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

Conditions

1. No deletion of packaging component or device.
2. The qualitative and quantitative composition of the packaging components/device and design specifications remain the same.
3. The specifications and quality control method are at least equivalent.
4. The sterilisation method and conditions remain the same, if applicable.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
2. For devices for medicinal products for human use, proof of CE marking.
3. Comparative table of current and proposed specifications, if applicable.

B.II.f) *Stability*

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

Conditions

1 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 or NTA volume 6B format for veterinary products, as appropriate). This must contain results of appropriate real time stability studies (covering the entire shelf life) conducted in accordance with the relevant stability guidelines on at least two pilot scale batches[1] of the finished product in the authorised packaging material and/or after first opening or reconstitution, as appropriate; where applicable, results of appropriate microbiological testing should be included.

   [1]Pilot scale batches can be accepted with a commitment to verify the shelf life on production scale batches.

2. Revised product information.
3. Copy of approved end of shelf life finished product specification and where applicable, specifications after dilution/reconstitution or first opening.

(*) *Note:* Extrapolation not applicable for biological/immunological medicinal product.

B.II.g) *Design Space*

B.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product, excluding biologicals, concerning	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) One or more unit operations in the manufacturing process of the finished product including the resulting in-process controls and/or test procedures		1, 2, 3	II
b) Test procedures for excipients/intermediates and/or the finished product.		1, 2, 3	II

Documentation

1. Results from product and process development studies (including risk assessment and multivariate studies, as appropriate) demonstrating that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the finished product has been achieved.
2. Description of the design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.
3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

B.II.g.2 Introduction of a post approval change management protocol related to the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
		1, 2	**II**

Documentation

1. Detailed description for the proposed change.
2. Change management protocol related to the finished product

B.II.g.3 Deletion of an approved change management protocol related to the finish product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	**1**	**IA_{IN}**

Conditions

1. The deletion of the approved change management protocol related to the finish product is not a result of unexpected events or out of specification results during the implementation of the change (s) described in the protocol.

Documentation

1. Justification for the proposed deletion.

B.III CEP/TSE/MONOGRAPHS

B.III.1 Submission of a new or updated Ph. Eur. certificate of suitability:	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
For an active substance **For a starting material/reagent/intermediate used in the manufacturing process of the active substance** **For an excipient**			
a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.			
1. New certificate from an already approved manufacturer	**1, 2, 3, 4, 5, 8**	**1, 2, 3, 4, 5**	**IA_{IN}**
2. Updated certificate from an already approved manufacturer	**1, 2, 3, 4, 8**	**1, 2, 3, 4, 5**	**IA**
3. New certificate from a new manufacturer (replacement or addition)	**1, 2, 3, 4, 5, 8**	**1, 2, 3, 4, 5**	**IA_{IN}**
b) European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/intermediate/or excipient			
1. New certificate for an active substance from a new or an already approved manufacturer	**3, 6**	**1, 2, 3, 4, 5**	**IA_{IN}**
2. New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	**3, 6**	**1, 2, 3, 4, 5**	**IA**
3. Updated certificate from an already approved manufacturer	**7**	**1, 2, 3, 4, 5**	**IA**

Conditions

1. The finished product release and end of shelf life specifications remain the same.

2. Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.

3. The manufacturing process of the active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.

4. For active substance only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier.

5. The active substance/starting material/reagent/intermediate/excipient is not sterile.

6. The substance is not included in a veterinary medicinal product for use in animal species susceptible to TSE.

7. For veterinary medicinal products: there has been no change in the source of material.

8. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.

Documentation

1. Copy of the current (updated) Ph. Eur. Certificate of Suitability.

2. In case of an addition of a manufacturing site, the variation application form should clearly outline the 'present' and 'proposed' manufacturers as listed in section 2.5 of the (Part IA) application form.

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

4. Where applicable, a document providing information of any materials falling within the scope of the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* including those which are used in the manufacture of the active substance/excipient. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.

   For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).

5. For active substance - a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the QP of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances - see the note under variation no. B.II.b.1. The manufacture of intermediates also require a QP declaration, while as far as any updates to certificates for active substances and intermediates are concerned, a QP declaration is only required if, compared to the previously registered version of the certificate, there is a change to the actual listed manufacturing sites.

B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Change of specification(s) of a former non-Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State			
1. Active substance	**1, 2, 3, 4, 5**	**1, 2, 3, 4, 5**	**IA_{IN}**
2. Excipient/active substance starting material	**1, 2,4**	**1, 2, 3, 4, 5**	**IA**
b) Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	**1, 2, 4, 5**	**1, 2, 3, 4**	**IA**
c) Change in specifications from a national pharmacopoeia of a Member State to the Ph. Eur.	**1, 4, 5**	**1, 2, 3, 4**	**IA**

Conditions

1. The change is made exclusively to comply with the pharmacopoeia.

2. Additional specifications to the pharmacopoeia for product specific properties are unchanged (e.g. particle size profiles, polymorphic form or e.g. bioassays, aggregates).

3. No significant changes in qualitative and quantitative impurities profile unless the specifications are tightened

4. Additional validation of a new or changed pharmacopoeial method is not required.

5. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

2. Comparative table of current and proposed specifications.

3. Batch analysis data on two production batches of the relevant substance for all tests in the new specification.

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. Where appropriate, batch analysis data (in a comparative tabulated format) on two production batches of the finished product containing the substance complying with the current and proposed specification and additionally, where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch. For herbal medicinal products, comparative disintegration data may be acceptable.

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 compliance with the updated monograph is implemented within six months of its publication and reference is made to the 'current edition' in the dossier of an authorised medicinal product.

B.IV MEDICAL DEVICES

B.IV.1 Change of a measuring or administration device	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Addition or replacement of a device which is not an integrated part of the primary packaging			
1. Device with CE marking	**1, 2, 3**	**1, 2, 4**	**IA_{IN}**
2. Device without CE marking for veterinary products only		**1, 3, 4**	**IB**
3. Spacer device for metered dose inhalers			**II**
b) Deletion of a device	**4, 5**	**1, 5**	**IA_{IN}**
c) Addition or replacement of a device which is an integrated part of the primary packaging			**II**

Conditions

1. The proposed measuring device must accurately deliver the required dose for the product concerned in line with the approved posology and results of such studies should be available.
2. The new device is compatible with the medicinal product.
3. The change should not lead to substantial amendments of the product information.
4. The medicinal product can still be accurately delivered.
5. For veterinary medicinal products, the device is not crucial for the safety of the person administering the product.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including description, detailed drawing and composition of the device material and supplier where appropriate, and including revised product information as appropriate.
2. Proof of CE marking.
3. Data to demonstrate accuracy, precision and compatibility of the device.
4. Samples of the new device where applicable (see NTA, Requirements for samples in the Member States).
5. Justification for the deletion of the device.

Note: For B.IV.1.c), applicants are reminded that any change which results in a 'new pharmaceutical form' requires the submission of an Extension application.

B.IV.2 Change in specification parameters and/or limits of a measuring or administration device for veterinary medicinal products	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter to the specification with its corresponding test method	**1, 2, 5**	**1, 2, 3, 4, 6**	**IA**
c) Widening of the approved specifications limits, which has a significant effect on the overall quality of the device			**II**
d) Deletion of a specification parameter that has a significant effect on the overall quality of the device			**II**
e) Addition of a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4, 6**	**IB**
f) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)		**1, 2, 5**	**IA**

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change should not be the result of unexpected events arising during manufacture.

3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same.
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
2. Comparative table of current and proposed specifications.
3. Details of any new analytical method and summary of validation data.
4. Batch analysis data on two production batches for all tests in the new specification.
5. Justification/risk-assessment showing that the parameter is non-significant.
6. Justification for the new specification parameter and the limits.

B.IV.3 Change in test procedure of a measuring or administration device for veterinary medicinal products	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor change to an approved test procedure	**1, 2**	**1, 2**	**IA**
b) Other changes to a test procedure (including replacement or addition)	**1, 3**	**1, 2**	**IA**
c) Deletion of a test procedure if an alternative test 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 test procedure is at least equivalent to the former test procedure.
2. The method of analysis should remain the same.
3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
4. An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA(IN) notification.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate)t, including a description of the analytical methodology and a summary of validation data.
2. Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

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

B.V.a) *PMF/VAMF*

B.V.a.1 Inclusion of a new, updated or amended Plasma Master File in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) First-time inclusion of a new Plasma Master File affecting the properties of the finished product			**II**
b) First-time inclusion of a new Plasma Master File not affecting the properties of the finished product		**1, 2, 3, 4**	**IB**
c) Inclusion of an updated/amended Plasma Master File when changes affect the properties of the finished product		**1, 2, 3, 4**	**IB**
d) Inclusion of an updated/amended Plasma Master File when changes do not affect the properties of the finished product	**1**	**1, 2, 3, 4**	**IA_{IN}**

Conditions

1. The updated or amended Plasma Master File has been granted a certificate of compliance with legislation of the Union in accordance with Annex I to Directive 2001/83/EC.

Documentation

1. Declaration that the PMF Certificate and Evaluation Report are fully applicable for the authorised product, PMF holder has provided the PMF Certificate, Evaluation report and PMF dossier to the MAH (where the MAH is different to the PMF holder), the PMF Certificate and Evaluation Report replace the previous PMF documentation for this Marketing Authorisation.
2. PMF Certificate and Evaluation Report.
3. An expert statement outlining all the changes introduced with the certified PMF and evaluating their potential impact on the finished products including product specific risk assessments.
4. The variation application form should clearly outline the 'present' and 'proposed' PMF EMEA Certificate (code number) in the MA dossier. When applicable, the variation application form should clearly list also all the other PMFs to which the medicinal product refers even if they are not the subject of the application.

B.V.a.2 Inclusion of a new, updated or amended Vaccine Antigen Master File in the marketing authorisation dossier of a medicinal product. (VAMF 2nd step procedure)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) First-time inclusion of a new Vaccine Antigen Master File			**II**
b) Inclusion of an updated/amended Vaccine Antigen Master File, when changes affect the properties of the finished product		**1, 2, 3, 4**	**IB**
c) Inclusion of an updated/amended Vaccine Antigen Master File, when changes do not affect the properties of the finished product	**1**	**1, 2, 3, 4**	**IA_{IN}**

Conditions

1. The updated or amended Vaccine Antigen Master File has been granted a certificate of compliance with legislation of the Union in accordance with Annex I to Directive 2001/83/EC.

Documentation

1. Declaration that the VAMF Certificate and Evaluation Report are fully applicable for the authorised product, VAMF holder has submitted the VAMF Certificate, Evaluation report and VAMF dossier to the MAH (where the MAH is different to the VAMF holder), the VAMF Certificate and Evaluation Report replace the previous VAMF documentation for this Marketing Authorisation.
2. VAMF Certificate and Evaluation Report.
3. An expert statement outlining all the changes introduced with the certified VAMF and evaluating their potential impact on the finished products including product specific risk assessments.
4. The variation application form should clearly outline the 'present' and 'proposed' VAMF EMEA Certificate (code number) in the MA dossier. When applicable, the variation application form should clearly list also all the other VAMFs to which the medicinal product refers even if they are not the subject of the application.

B.V.b) *Referral*

B.V.b.1 Update of the quality dossier following a Commission Decision following the procedure of Article 30 or 31 of Directive 2001/83/EC or Article 34 or 35 of Directive 2001/82/EC (referral procedure)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) The change implements the outcome of the referra (*)		**1**	**IA_{IN}**
b) The harmonisation of the quality dossier was not part of the referral and the update is intended to harmonise it			**II**

Documentation

1. Attached to the cover letter of the variation application: A reference to the Commission Decision concerned.

(*) *Note:* Applies in cases where the marketing authorisation holder(s) need to take steps to allow the Member States to comply with the Commission decision within 30 days after its notification in accordance with Article 34(3) of Directive 2001/83/EC and Article 38(3) of Directive 2001/82/EC.

B.V.c) *Change management protocol*

B.V.c.1 Update of the quality dossier to implement changes, requested by the EMEA/National Competent Authority, following assessment of a change management protocol	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) The implementation of the change requires no further supportive data	**1**	**1, 2, 4**	**IA_{IN}**
b) The implementation of the change requires further supportive data		**1, 2, 3, 4**	**IB**
c) Implementation of a change for a biological/immunological medicinal product		**1, 2, 3, 4, 5**	**IB**

Conditions

1. The proposed change has been performed fully in line with the approved change management protocol, which requires its immediate notification following implementation.

Documentation

1. Reference to the approved change management protocol.
2. Declaration that the change is in accordance with the approved change management and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.
3. Results of the studies performed in accordance with the approved change management protocol.
4. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
5. Copy of approved specifications of the active substance or the finished product.

C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES

C.I HUMAN AND VETERINARY MEDICINAL PRODUCTS

C.I.1 Change in the Summary of Product Characteristics, Labelling or Package Leaflet following a procedure in accordance with Article 30 or 31 of Directive 2001/83/EC or Article 34 or 35 of Directive 2001/82/EC (referral procedure)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) The medicinal product is covered by the defined scope of the referral (*)		**1, 2, 3**	**IA_{IN}**
b) The medicinal product is not covered by the defined scope of the referral but the change implements the outcome of the referral and no new additional data are submitted by the MAH		**1, 2, 3**	**IB**
c) The medicinal product is not covered by the defined scope of the referral but the change implements the outcome of the referral with new additional data submitted by the MAH		**1, 3**	**II**

Documentation

1. Attached to the cover letter of the variation application: A reference to the Commission Decision concerned with the annexed Summary of Product Characteristics, Labelling or Package Leaflet.

2. A declaration that the proposed Summary of Product Characteristics, Labelling and Package Leaflet is identical for the concerned sections to that annexed to the Commission Decision on the referral procedure for the reference medicinal product.

3. Revised product information.

(*) *Note:* Applies in cases where the marketing authorisation holder(s) need to take steps to allow the Member States to comply with the Commission decision within 30 days after its notification in accordance with Article 34(3) of Directive 2001/83/EC and Article 38(3) of Directive 2001/82/EC.

C.I.2 Change in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Implementation of change(s) for which no new additional data are submitted by the MAH		**1, 2**	**IB**
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH (e.g. comparability)			**II**

Documentation

1. Attached to the cover letter of the variation application: EMEA/NCA request, if applicable.

2. Revised product information.

C.I.3 Implementation of change(s) requested by the EMEA/National Competent Authority following the assessment of an Urgent Safety Restriction, class labelling, a Periodic Safety Update report, Risk Management Plan, Follow Up Measure/Specific Obligation, data submitted under Article 45/46 of Regulation (EC) No 1901/2006, or amendments to reflect a competent authority Core SPC	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH		**1, 2**	**IB**
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH			**II**

Documentation

1. Attached to the cover letter of the variation application: EMEA/NCA request with attached relevant assessment report, if available.

2. Revised product information.

Note: MAHs are reminded that once new information becomes available which might entail the variation of the MA, this should be submitted forthwith as a variation to the competent authorities, rather than awaiting the assessment of those data through one of the procedures mentioned above.

C.I.4 Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

C.I.5 Change in the legal status of a medicinal product for centrally authorised products	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) For generic/hybrid/biosimilar medicinal products following an approved legal status change of the reference medicinal product		**1, 2**	**IB**
b) All other legal status changes			**II**

Documentation

1 Attached to the cover letter of the variation application: proof of authorisation of the legal status change (e.g. reference to the Commission Decision concerned).

2. Revised product information.

Note: For Nationally Authorised Products approved via MRP/DCP, the change of the legal status is to be handled at national level (not via a MRP variation).

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

Note: Where the addition or modification of a therapeutic indication takes place in the context of the implementation of the outcome of a referral procedure or of changes to the product information of a generic/hybrid/biosimilar product following assessment of the same change for the reference product, variations C.I.1 and C.I.2 apply, respectively.

C.I.7 Deletion of:	Conditions to be fulfilled	Documentation to be supplied	Procedure 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.I.8 Introduction of a new Pharmacovigilance system	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) which has not been assessed by the relevant national competent authority/EMEA for another product of the same MAH			**II**
b) which has been assessed by the relevant national competent authority/EMEA for another product of the same MAH (*)		**1**	**IB**

Documentation

1. The new Detailed Description of the Pharmacovigilance System (DDPS).

(*) *Note:* This variation covers the situation where the applicability of an already assessed Pharmacovigilance System will have to be assessed for the new MAs concerned (e.g. at time of transfer of MA).

C.I.9 Changes to an existing pharmacovigilance system as described in the DDPS.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Change in the QPPV	**1**	**1**	**IA_{IN}**
b) Change in the contact details of the QPPV	**1**	**2**	**IA_{IN}**
c) Change of the back-up procedure of the QPPV	**1**	**2**	**IA_{IN}**
d) Change in the safety database (e.g. Introduction of a new safety database including transfer of safety data collection and/or analysis and reporting to the new system)	**1, 2, 3**	**2**	**IA_{IN}**
e) Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DDPS, in particular where the electronic reporting of ICSRs, the main databases, signal detection, or the compilation of PSURs is subcontracted	**1**	**2**	**IA_{IN}**

f) Deletion of topics covered by written procedure(s) describing pharmacovigilance activities	**1**	**2**	**IA_{IN}**
g) Change of the site undertaking pharmacovigilance activities	**1**	**2**	**IA_{IN}**
h) Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system (e.g. change of the major storage/archiving location, administrative changes, update of acronyms, naming changes of functions/procedures).	**1**	**2**	**IA**
i) Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	**4**	**2, 3**	**IA_{IN}**

Conditions

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

Documentation

1. Latest version of the DDPS, including a) summary CV of the new QPPV, b) proof of QPPV EudraVigilance registration, and c) a new statement of the MAH and the QPPV regarding their availability and the means for notification of adverse reactions signed by the new QPPV and the MAH, and reflecting any other consequential changes, e.g. to the organisation chart.
2. Latest version of the DDPS and/or latest version of product(s) specific addendum(s), as applicable. For b) if the contact details of the QPPV were not initially included in the DDPS, submission of a revised DDPS version is not required/only application form/notification to be provided.
3. Reference of the application/procedure and product in which the change(s) were accepted.

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

C.II VETERINARY MEDICINAL PRODUCT – SPECIFIC CHANGES

C.II.1 Variations concerning a change to or addition of a non-food producing target species.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

C.II.2 Deletion of a food producing or non-food producing target species.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Deletion as a result of a safety issue			**II**
b) Deletion not resulting from a safety issue		**1, 2**	**IB**

Documentation

1. Justification for the deletion of the target species
2. Revised product information

C.II.3 Changes to the withdrawal period for a veterinary medicinal product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

C.II.4 Variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine against avian influenza, foot-and-mouth disease or bluetongue.	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II

C.II.5 Variations concerning the replacement of a strain for a veterinary vaccine against equine influenza.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II

C.II.6 Changes to the labelling or the package leaflet which are not connected with the summary of product characteristics.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			IB

Note: This Annex does not deal with changes to the labelling or the package leaflet which are not connected with the summary of product characteristics for medicinal products for human use, as Article 61(3) of Directive 2001/83/EC provides for a specific notification procedure for such changes. As Directive 2001/82/EC does not contain a corresponding provision for veterinary medicinal products, such changes are covered by this variation.

D. **PMF/VAMF**

D.1 Change in the name and/or address of the VAMF certificate holder	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA_{IN}

Conditions

1. The VAMF certificate holder shall remain the same legal entity.

Documentation

1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.

D.2 Change in the name and/or address of the PMF certificate holder	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA_{IN}

Conditions

1. The PMF certificate holder shall remain the same legal entity.

Documentation

1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.

D.3 Change or transfer of the current PMF certificate holder to a new PMF certificate holder -i.e. different legal entity	Conditions to be fulfilled	Documentation to be supplied	Procedure 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 'EMEA Plasma Master File (PMF) Certificate of compliance with Community legislation'.
3. Proof of establishment of the new holder (Excerpt of the commercial register and the English translation of it) - signed by both companies.
4. Confirmation of the transfer of the complete PMF documentation since the initial PMF certification to the transferee - signed by both companies.
5. Letter of Authorisation including contact details of the person responsible for communication between the competent authority and the PMF holder - signed by the transferee.
6. Letter of Undertaking to fulfil all open and remaining commitments (if any) - signed by the transferee.

D.4 Change in the name and/or address of a blood establishment including blood/plasma collection centres	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1, 2	1, 2, 3	IA

Conditions

1. The blood establishment shall remain the same legal entity.
2. The change shall be administrative (e.g. merger, take over); change in the name of the blood establishment/collection centre provided the blood establishment shall remain the same.

Documentation

1. Signed declaration that the change does not involve a change of the quality system within the blood establishment.
2. Signed declaration that there is no change in the list of the collection centres.
3. Updated relevant sections and annexes of the PMF dossier.

D.5 Replacement or addition of a blood/plasma collection centre within a blood establishment already included in the PMF	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2, 3	IB

Documentation

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

D.6 Deletion or change of status (operational/non-operational) of establishment(s)/centre(s) used for blood/plasma collection or in the testing of donations and plasma pools	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1, 2	1	IA

Conditions

1. The reason for deletion or change of status should not be related to a GMP issue.
2. The establishments(s)/centre(s) should comply with the legislation in terms of inspections in case of change of status from non-operational to operational.

Documentation

1. Updated relevant sections and annexes of the PMF dossier.

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

D.8 Replacement or addition of a blood centre for testing of donations and/or plasma pools within an establishment already included in the PMF	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2	IB

Documentation

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

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

D.10 Replacement or addition of a new blood establishment or centre(s) in which storage of plasma is carried out	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2	IB

Documentation

1. Statement that the storage centre is working following the same SOPs as the already accepted establishment.
2. Updated relevant sections and annexes of the PMF dossier.

D.11 Deletion of a blood establishment or centre(s) in which storage of plasma is carried out	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA

Conditions

1. The reason for deletion should not be related to a GMP issues.

Documentation

1. Updated relevant sections and annexes of the PMF dossier.

D.12 Replacement or addition of an organisation involved in the transport of plasma.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1	IB

Documentation

1. Updated relevant sections and annexes of the PMF dossier, including a list of all the blood establishments using this transport organisation, a summary of the system in place to ensure that the transport is performed under appropriate conditions (time, temperature and GMP compliance) and confirmation that transport conditions are validated.

D.13 Deletion of an organisation involved in the transport of plasma	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA

Conditions

1. The reason for deletion should not be related to GMP issues.

Documentation

1. Updated relevant sections and annexes of the PMF dossier.

D.14 Addition of a CE-marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1, 2	IA

Conditions

1. The new test kit is CE-marked.

Documentation

1. List of testing site(s) where the kit is used.

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

D.15 Addition of a non-CE marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The new test kit has not previously been approved in the PMF for any blood centre for testing of donations			II
b) The new test kit has been approved in the PMF for other blood centre(s) for testing of donations		1, 2	IA

Documentation

1. List of testing centre(s) where the kit is currently used and a list of testing centre(s) where the kit will be used.

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

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

D.17 Introduction or extension of inventory hold procedure.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA

Conditions

1. The inventory hold procedure is a more stringent procedure (e.g. release only after retesting of donors).

Documentation

1. Updated relevant sections of the PMF dossier, including the rationale for introduction or extension of inventory hold period, the sites where the inventory hold takes place and for changes to procedure, a decision tree including new conditions.

D.18 Removal of inventory hold period or reduction in its length.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1	IB

Documentation

1. Updated relevant sections of the PMF dossier.

D.19 Replacement or addition of blood containers (e.g. bags, bottles)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The new blood containers are CE-marked	1, 2	1	IA
b) The new blood containers are not CE-marked			II

Conditions

1. The container is CE-marked.
2. The quality criteria of the blood in the container remain unchanged.

Documentation

1. Updated relevant sections and annexes of the PMF dossier, including the name of container, manufacturer, anticoagulant solution specification, confirmation of CE-mark and the name of the blood establishments where the container is used.

D.20 Change in storage/transport	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) storage and/or transport conditions	1	1	IA
b) maximum storage time for the plasma	1, 2	1	IA

Conditions

1. The change should tighten the conditions and be in compliance with Ph. Eur. requirements for Human Plasma for Fractionation.
2. The maximum storage time is shorter than previously.

Documentation

1. Updated relevant sections and annexes of the PMF dossier, including detailed description of the new conditions, confirmation of validation of storage/transport conditions and the name of the blood establishment(s) where the change takes place (if relevant).

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

D.22 Change in the plasma pool preparation (e.g. manufacturing method, pool size, storage of plasma pool samples)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1	IB

Documentation

1. Updated relevant sections of the PMF dossier.

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