21 April 2023
EMA/CMDv/7381/2021 - Rev.2

# Guidance on the details of the classification of variations requiring assessment according to Article 62 of Regulation (EU) 2019/6 for veterinary medicinal products and on the documentation to be submitted pursuant to those variations

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# Executive Summary

This guidance is intended to explain the practice of Articles 60 to 68 of Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products, laying down rules for the placing on the market, manufacturing, import, export, supply, distribution, pharmacovigilance, control and use of veterinary medicinal products and to categorise the variations requiring assessment. The Annex to this guidance provides a list of variations, which require assessment according to Article 62 of Regulation (EU) 2019/6 and indicates, where appropriate, the timetable proposed to be applied, the data to be submitted and how this data should be documented. The Annex to this guidance will be regularly updated, taking into account the recommendations provided in accordance with section 7 of this guidance as well as scientific and technical progress. This guidance shall come into effect from the date of application of Regulation (EU) 2019/6.

# 1. Introduction

The objective of this guidance is to provide details on variations requiring assessment, i.e. those not listed in the Commission Implementing Regulation (EU) 2021/17 of 8 January 2021 establishing a list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council, hereafter referred to as the Implementing Regulation.

According to Article 62(1) of Regulation (EU) 2019/6, where a variation is not included in the Implementing Regulation, the marketing authorisation holder shall submit an application for a variation requiring assessment to the competent authority which has granted the marketing authorisation or to the Agency, as applicable.

This guidance is intended to

- establish a specific veterinary variation guidance;
- introduce, for variations requiring assessment according to Article 62(1) of Regulation (EU) 2019/6, a variation code system and its documentation requirements;
- utilise existing knowledge to include all known variations;
- identify variations that fundamentally alter the terms of the marketing authorisation and that can either be granted a marketing authorisation or be included in the initial marketing authorisation to which it relates (changes of active substance(s), strength, pharmaceutical form, route of administration or food producing target species);
- reflect the different levels of complexity of variations requiring assessment, as such generally enabling shorter assessment timetables for less complex variations and longer timetables for changes of active substance(s), strength, pharmaceutical form, route of administration or food producing target species and other more complex variations.

# 2. Scope

This guidance concerns variations, which require assessment i.e. those, which are not listed in the Implementing Regulation. As laid down in Article 4(39) of Regulation (EU) 2019/6 'variation' means a change to the terms of the marketing authorisation for veterinary medicinal products as referred to in Article 36 of Regulation (EU) 2019/6. The marketing authorisation(s) concerned may be valid throughout the Union ('centralised marketing authorisation'), in a single Member State ('national marketing authorisation'), or in several Member States ('decentralised marketing authorisations, DCP'),

including those resulting from a mutual recognition procedure (MRP) or subsequent recognition procedure (SRP, formerly Repeat Use Procedure).

# 3. Legal basis

This guidance shall be read in conjunction with Articles 62 to 68 of Regulation (EU) 2019/6.

# 4. Definitions

Definitions relevant to this guidance are provided in Regulation (EU) 2019/6. In addition, for the purpose of this guidance, marketing authorisation holders belonging to the same mother company or group of companies and marketing authorisation holders having concluded agreements or exercising concerted practices concerning the placing on the market of the relevant medicinal product have to be taken as the same marketing authorisation holder[1] ("holder").

# 5. Types of variations

Articles 61 and 62 of Regulation (EU) 2019/6 foresee two types of variations: Those not requiring assessment and those requiring assessment.

**i. Variations not requiring assessment – Article 61**

According to Article 61 of Regulation (EU) 2019/6, any variation that is listed in the Implementing Regulation shall follow the procedure laid down in that article. The Implementing Regulation determines the relevant requirements (conditions and documentation) that shall be fulfilled.

**ii. Variations requiring assessment – Article 62**

According to Article 62(1) Regulation (EU) 2019/6, any variation that is not listed in the Implementing Regulation requires an application for variation requiring assessment. The rules provided for in Articles 62 to 68 of Regulation (EU) 2019/6 shall be applied.

# 6. Variations arising from those listed in Commission Implementing Regulation (EU) 2021/17 which do not meet the requirements laid down therein

Where the general description of a variation is listed in the Implementing Regulation, but at least one of the relevant requirements laid down therein is not fulfilled, that particular variation cannot be executed as a variation not requiring assessment. Such variation has to be submitted as a variation requiring assessment, subject to the procedures according to Articles 62 to 68 of Regulation (EU) 2019/6.

That particular variation should follow the rules provided hereunder:

1. Where the particular variation is listed in the Annex to this guidance, it should be classified in accordance with the Annex to this guidance.

2. Where the particular variation is not specifically listed in the Annex to this guidance, it should be classified under the relevant code level within the appropriate chapter of this Annex, using the "z"-

[1] Commission communication on the Community marketing authorisation procedures for medicinal products 98/C 229/03 OJ C 229, 22.7.1998, p. 4 - link

variation. Further information on the "z"-variations is provided in section 9 Explanation of the Annex to this guidance.

# 7. Classification of additional, new variations not already listed

While very comprehensive, the Annex is not an exhaustive list of variations requiring assessment.

As such, where a particular variation is not listed in the Annex to this guidance, and it is not listed in the Implementing Regulation, that particular variation shall follow the rules provided for in Article 62(1) of Regulation (EU) 2019/6. The variation should be classified under the relevant code level of the appropriate chapter of the Annex, using the "z"-variation. Further information on the "z"-variations is provided in section 9 Explanation of the Annex to this guidance.

Where a particular variation is neither listed in the Implementing Regulation, nor in the Annex to this guidance, the CMDv in consultation with the EMA may deliver, upon request, a recommendation concerning the type of variation, the classification code and conditions and documentation requirements as relevant. Where relevant, any recommendation for a specific variation requiring assessment delivered pursuant to the CMDv and EMA classification procedure should be followed after the Annex of this guidance and the electronic Application Form have been updated accordingly. This guidance will be regularly updated to reflect experience gained and inclusion of variations not previously listed.

# 8. Timetables for variation procedures

In accordance with Article 66(3) of Regulation (EU) 2019/6 an assessment report or opinion shall be prepared within 60 days of receipt of a valid application of a variation requiring assessment. This period may be extended to 90 days for a more complex procedure.

Acknowledging that variations requiring assessment may have different levels of complexity and considering the timeframes within which variations requiring assessment are to be completed, this guidance allows a third shorter timetable for less complex procedures. The relevant timetables for each variation category are included in the Annex as a separate column.

In the column "timetable" of the annexed tables, the following abbreviations are used to indicate the review time generally considered appropriate:

- "R" for Reduced timetable
- "S" for Standard timetable
- "E" for Extended timetable

However, where appropriate, the competent authority, the Agency, the competent authority agreed in accordance with Article 65(3) of Regulation (EU) 2019/6, or the competent authority in the Reference Member States, as applicable, may decide to use other timetable than those detailed in this guideline.

Grouped variations requiring assessment will be processed according to the longest timetable applicable to any of the included variations.

For variations requiring assessment that concern products authorised in the national, DCP, MRP or SRP procedure, the procedural handling is laid down in the CMDv Best Practice Guide for Variations requiring assessment. This includes a description of all the relevant steps from the submission of an application for a variation to the final outcome of the procedure on the application.

# 9. Explanation of the Annex to this guidance

The Annex to this guidance provides for the classification of variations requiring assessment in accordance with Regulation (EU) 2019/6. It should be regarded as being complementary to the classifications laid down in the Implementing Regulation which details variations considered to not require assessment.

Thus the classification codes provided for in the Annex to this guidance start with the capital letter "E" and they are a continuation of the classification codes used in the Implementing Regulation which use the classification codes "A", "B", "C" and "D".

The Annex to this guidance consists of five chapters classifying variations related to:

- E. Administrative changes,
- F. Quality changes,
- G. Safety, Efficacy and Pharmacovigilance changes,
- H. VAMF or, PTMF changes,
- Changes of active substance(s), strength, pharmaceutical form, route of administration or food producing target species (variations that fundamentally alter the terms of the marketing authorisation and that can either be granted a marketing authorisation or be included in the initial marketing authorisation to which it relates),
- Where reference is made to a specific variation in this Annex, the variation in question should be referenced using the following structure: X.N.x.n.x.n ("variation classification code"),
- X refers to the capital letter of the chapter in this Annex as described above (e.g. "E"),
- N refers to the roman number of the subchapter within a chapter where the variation is included (e.g. I, II, III…),
- x refers to the letter of the topic within a chapter where the variation is included (e.g. a, b, c…),
- n refers to the number given for a subtopic in this Annex to a specific variation (e.g. 1, 2, 3…),
- For some variations further levels are necessary: Category (e.g. a, b, c…) and subcategory (e.g. 1, 2, 3,…),
- On the appropriate level within a chapter, a "z"-variation has been included in order to provide for the following cases:

a) Variations which are listed in the Annex to the Implementing Regulation, but at least one of the requirements laid down in the Implementing Regulation is not fulfilled;

b) Variations that are neither listed in the Annex to this guidance nor in that of the Implementing Regulation.

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

When several minor changes are taking place (e.g. to the same method or process or material) at the same time or in cases of a major update of the quality information for the active substance or the

finished product, the applicant should take into account the overall impact of these changes on the quality, safety or efficacy of the medicinal product when considering the appropriate classification and submit them accordingly.

Requirements for supporting data for particular variations will depend on the exact nature of the change and are not specified for all variations, however, where specified the appropriate data is to be provided. In most cases this is to facilitate the reduced timetable. In all cases where the change impacts on the contents of the dossier the variation application should include amendment of the relevant section(s) of the dossier.

Furthermore, if a variation leads to a revision of the summary of product characteristics, labelling or package leaflet (jointly referred to as 'the product information'), this change is considered part of that variation. For veterinary medicinal products authorised through the centralised, DCP, MRP and SRP procedures the updated common English product information has to be submitted as part of the initial variation application with relevant translations provided at the end of the procedure (centralised) or after the end of the European phase of the procedure (EoP) (DCP, MRP and SRP). For purely nationally authorised products only Product Information (PI) in the language of the member state is required and should be provided with the initial variation application. Mock-ups or specimens should be provided to the Reference Member State, the national competent authority or the Agency if required.

It is not necessary to notify the competent authorities of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State when the version number of the monograph is not specified in the dossier and it is refered to as "current edition" or similar. Applicants are reminded that compliance with the updated monograph should be implemented within six months of its publication.

Any change to the content of the data that supports a European Pharmacopoeia Certificate of Suitability, should be submitted to the European Directorate for the Quality of Medicines (EDQM). Such changes may result in a revison of the certificate. When a revised certificate, or consequential changes to other sections of the dossier are implemented at the manufacturing site any marketing authorisation concerned must be updated accordingly by submittiung an appropriate variation.

Where the Annex to this guidance refers to 'changes to the marketing authorisation dossier', it should be understood as addition, replacement or deletion, unless specifically indicated. If amendments to the dossier only concern editorial changes, such changes should generally not be submitted as a separate variation, but they can be included in a variation concerning that part of the dossier. In such cases the changes should be clearly identified in the application form as editorial changes and a declaration that the content of the concerned part of the dossier has not been changed by the editorial changes beyond the scope of the variation submitted should be provided. It should be noted that editorial changes include the removal of obsolete or redundant text but not the removal of specification parameters or manufacturing descriptions.

The Annex to this guidance will be updated regularly, taking into account the recommendations provided in accordance the relevant processes, such as those refered to in section 7, as well as scientific and technical progress.

# 10. References

Regulation (EU) 2019/6 of the European Parliament and of the Council of 11 December 2018 on veterinary medicinal products, laying down rules for the placing on the market, manufacturing, import, export, supply, distribution, pharmacovigilance, control and use of veterinary medicinal products.

Commission Implementing Regulation (EU) 2021/17 of 8 January 2021 establishing a list of variations not requiring assessment in accordance with Regulation (EU) 2019/6 of the European Parliament and of the Council.

# 11. Annex

## CHAPTER E. ADMINISTRATIVE CHANGES

| E.I Changes to date of the audit to verify GMP compliance of the manufacturer of the active substance | Documentation to be supplied | Timetable |
|---|---|---|
| | **1** | **R** |
| **Documentation** | | |
| 1. Written confirmation from the manufacturer of the finish product stating verification of compliance of the manufacturer of the active substance with principles and guidelines of good manufacturing practices. | | |
| Note: this variation does not apply when the information has been otherwise transmitted to the authorities (e.g. through the so-called 'QP declaration'). | | |

| E.z Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance | Documentation to be supplied | Timetable |
|---|---|---|
| | | **R** |

## CHAPTER F. QUALITY CHANGES

### *F.I ACTIVE SUBSTANCE*

#### F.I.a) Manufacture

| F.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier | Documentation to be supplied | Timetable |
|---|---|---|
| **a) Introduction of a manufacturer of the active substance supported by an ASMF** | | **S** |
| **b) 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** | | **S** |
| **c) New manufacturer of material for which an assessment is required of viral safety and/or TSE risk** | | **S** |
| **d) The change relates to a biological/immunological active substance or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product** | | **S** |
| **e) Introduction of a new manufacturer of the active substance that is not supported by an ASMF and requires significant update to the relevant active substance section of the dossier** | | **S** |
| **f) Addition of an alternative sterilisation site for the active substance using a Ph. Eur. method** | **1, 2, 3, 4** | **R** |
| **g) Changes to quality control testing arrangements for a biological active substance: replacement or addition of a site where batch control/testing including a biological / immunological / immunochemical method takes place** | | **S** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | |
| 1. 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. | | |
| 2. 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. | | |

| | |
|---|---|
| 3. | The variation application form should clearly outline the "present" and "proposed" manufacturers as listed in the application form for marketing authorisation. |
| 4. | Proof that the proposed site is appropriately authorised for the pharmaceutical form or product or manufacturing operation concerned, i.e.:<br>For a manufacturing site within the EU/EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMDP database will suffice.<br>For a manufacturing site outside the EU/EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority.<br>For a manufacturing site outside the EU/EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EU/EEA. A reference to the EudraGMDP database will suffice. |

| **F.I.a.2 Changes in the manufacturing process of the active substance** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) 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** | | **S** |
| **b) The change refers to a biological / immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological substance, which may have a significant impact on the quality, safety and efficacy of the medicinal product and is not related to a protocol** | | **S** |
| **c) The change relates to a herbal medicinal product and there is a change to any of the following: geographical source, manufacturing route or production** | | **S** |
| **d) Minor change to the restricted part of an Active Substance Master File** | **1, 2, 3, 4** | **R** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

| **Documentation** | |
|---|---|
| 1. | Amendment of the approved Active Substance Master File, 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 ASMF Holder that there is no change in qualitative and quantitative impurity profile or in physico-chemical properties, that the synthetic route remains the same and that the specifications of the active substance or intermediates are unchanged. |
| Note: For F.I.a.2.a: 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. | |

| F.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance | Documentation to be supplied | Timetable |
|---|---|---|
| **a) The change requires assessment of the comparability of a biological/immunological active substance** | | **S** |
| **b) The scale for a biological/immunological active substance is increased/decreased without process change (e.g. duplication of line)** | **1, 2, 3** | **R** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | |
| 1. The batch numbers of the tested batches having the proposed batch size. | | |
| 2. 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). | | |
| 3. Copy of approved specifications of the active substance (and of the intermediate, if applicable). | | |

| F.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance | Documentation to be supplied | Timetable |
|---|---|---|
| **a) Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the active substance** | | **S** |
| **b) Deletion of an in-process test which may have a significant effect on the overall quality of the active substance** | | **S** |
| **c) Addition or replacement of an in-process test as a result of a safety or quality issue** | **1, 2, 3, 4** | **R** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | |
| 1. Comparative table of current and proposed in-process tests. | | |
| 2. Details of any new non-pharmacopoeial analytical method and validation data, where relevant. | | |
| 3. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the active substance for all specification parameters. | | |
| 4. Justification from the MAH or ASMF Holder as appropriate for the new in-process test and limits. | | |

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

| F.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 | Documentation to be supplied | Timetable |
|---|---|---|
| **a) Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product** | | **S** |

| | | | |
|---|---|---|---|
| **b)** | **Change outside the approved specifications limits range for the active substance** | | **S** |
| **c)** | **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** | | **S** |
| **d)** | **Addition or replacement (excluding biological or immunological substance) of a specification parameter with its corresponding test method as a result of a safety or quality issue** | **1, 2, 3, 4, 5** | **R** |
| **e)** | **Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the active substance, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country** | **1, 2, 3, 4, 5** | **R** |
| **f)** | **Removal of level of testing level performed by the finished product manufacturer on receipt of the drug substance batches from the dossier(1)** | | **R** |
| **g)** | **Change in the testing frequency of specification parameter, from routine testing to skip or periodic testing** | | **R** |
| **z)** | **Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

**Documentation**

| | |
|---|---|
| 1. | Comparative table of current and proposed specifications. |
| 2. | Details of any new analytical method and validation data, where relevant. |
| 3. | Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the relevant substance for all specification parameters. |
| 4. | 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. |
| 5. | Justification from the MAH or ASMF Holder as appropriate of the new specification parameter and the limits. |

(1) If information on the level of testing performed by the finished product manufacturer on receipt of the drug substance batches is already present in the approved registration dossier, the applicant is advised to apply for a F.I.b.1.g variation to remove this information from the dossier.

The level of testing performed by the finished product manufacturer on receipt of batches of the drug substance is considered to be a GMP issue and therefore information on whether the finished product manufacturer performs all of the tests listed in the approved specifications or accepts some of the results based on the certificate of analysis provided by the drug substance manufacturer should not be included in the approved dossier. The level of testing performed by the finished product manufacturer on receipt of batches of the drug substance will be subject to review during a GMP inspection. The drug substance specifications applied by the finished product manufacturer should, however, continue to be stated in the dossier.

| **F.I.b.2 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance** | | **Documentation to be supplied** | **Timetable** |
|---|---|---|---|
| **a)** | **Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological active substance** | | **S** |

| | | |
|---|---|---|
| **b) Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate** | **1, 2** | **R** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | |
| 1. 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. | | |

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

| **F.I.c.1 Change in immediate packaging of the active substance** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances** | | **S** |
| **b) Liquid active substances (non sterile)** | **1, 2, 3, 4** | **R** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | |
| 1. 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. | | |
| 2. 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. | | |
| 3. The results of stability studies that have been carried out under VICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved retest period (with proposed action). | | |
| 4. Comparison of the current and proposed immediate packaging specifications, if applicable. | | |

| F.I.c.2 Change in the specification parameters and/or limits of the immediate packaging of the active substance | Documentation to be supplied | Timetable |
|---|---|---|
| **a) Addition or replacement of a specification parameter as a result of a safety or quality issue** | **1, 2, 3, 4** | **R** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | |
| 1. Comparative table of current and proposed specifications. | | |
| 2. Details of any new analytical method and validation data, where relevant. | | |
| 3. Batch analysis data on two batches of the immediate packaging for all specification parameters. | | |
| 4. Justification from the marketing authorisation holder or the ASMF Holder, as appropriate, of the new specification parameter and the limits. | | |

| F.I.c.3 Change in test procedure for the immediate packaging of the active substance | Documentation to be supplied | Timetable |
|---|---|---|
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

**F.I.d) Stability**

| F.I.d.1 Change in the re-test period/storage period of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier | Documentation to be supplied | Timetable |
|---|---|---|
| **a) Extension of the retest period based on extrapolation of stability data not in accordance with VICH guidelines*** | | **S** |
| **b) Extension of storage period of a biological/immunological active substance not in accordance with an approved stability protocol** | | **S** |
| **c) Extension or introduction of a re-test period/storage period supported by real time data** | **1, 2, 3** | **R** |
| **Documentation** | | |
| 1. 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 | | |

| F.I.d.2 Change in the storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier | Documentation to be supplied | Timetable |
|---|---|---|
| **a) Change in storage conditions of biological/immunological active substances/reference standards, when the stability studies have not been performed in accordance with a currently approved stability protocol** | | **S** |
| **b) Change in storage conditions of the active substance/reference standard** | **1, 2, 3** | **R** |
| **Documentation** | | |
| 1. 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. | | |

| F.I.d.z Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance | Documentation to be supplied | Timetable |
|---|---|---|
| | | **R** |

**F.I.e) Design Space and post-approval change management protocols**

| F.I.e.1 Introduction of a new design space or extension of an approved design space for the active substance, concerning: | Documentation to be supplied | Timetable |
|---|---|---|
| **a) One unit operation in the manufacturing process of the active substance including the resulting in-process controls and/or test procedures** | **1, 2** | **S** |
| **b) Test procedures for starting materials/reagents/ intermediates and/or the active substance** | **1, 2** | **S** |
| **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. | | |

| F.I.e.2 Changes to a post approval change management protocol related to the active substance | Documentation to be supplied | Timetable |
|---|---|---|
| **a) Introduction of a post approval change management protocol related to the active substance** | **1, 2** | **S** |

| | | |
|---|---|---|
| **b) Major changes to an approved change management protocol** | | **S** |
| **c) Implementation of changes foreseen in an approved change management protocol** | | |
| **1. The implementation of the change requires further supportive data** | **3, 4, 5** | **R** |
| **2. Implementation of a change for a biological/immunological medicinal product** | **3, 4, 5, 6** | **R** |

| **Documentation** | |
|---|---|
| 1. | Detailed description for the proposed change. |
| 2. | Change management protocol related to the active substance. |
| 3. | Reference to the approved change management protocol. |
| 4. | 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. |
| 5. | Results of the studies performed in accordance with the approved change management protocol. |
| 6. | Copy of approved specifications of the active substance. |

| **F.I.e.z Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| | | **R** |

**F.I.f) Other changes to the active substance**

| **F.I.f.1 Substantial changes in the updated version of the ASMF or the active substance part of the dossier** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| | | **S** |
| Note: The update can be submitted as a grouped application which will be processed according to the longest timetable of the included variations. However, in case of substantial changes in the updated version of this part of the dossier or the ASMF it is recommended to submit a single variation under category F.I.f.1 | | |

## *F.II. FINISHED PRODUCT*

### F.II.a) Description and composition

| **F.II.a.1 Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking.** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) Changes in scoring/break lines intended to divide into equal doses** | **1, 2, 3** | **R** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | |
| 1. Detailed drawing or written description of the current and new appearance. | | |
| 2. Samples of the finished product where applicable. | | |
| 3 Results of the appropriate Ph. Eur tests demonstrating equivalence in characteristics/correct dosing. | | |

| **F.II.a.2 Change in the shape or dimensions of the pharmaceutical form** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) Gastro-resistant, modified or prolonged release pharmaceutical forms and scored tablets intended to be divided into equal doses** | **1, 2, 3, 4, 5** | **R** |
| **b) Addition of a new kit for a radiopharmaceutical preparation with another fill volume*** | | **S** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | |
| 1. Detailed drawing of the current and proposed situation. | | |
| 2. Comparative dissolution data on at least one pilot batch of the current and proposed dimensions (no significant differences regarding comparability see the relevant guidance on bioavailability/bioequivalence). For herbal medicinal product comparative disintegration data may be acceptable. | | |
| 3. Justification for not submitting a new bioequivalence study according to the relevant guidance on Bioavailability/bioequivalence. | | |
| 4. Samples of the finished product where applicable. | | |
| 5. Results of the appropriate Ph. Eur tests demonstrating equivalence in characteristics/correct dosing. | | |
| *Note: Marketing authorisation holders are reminded that any change to the "strength" of the medicinal product is classified as a variation under chapter I of this annex. | | |

| **F.II.a.3 Changes in the composition (excipients) of the finished product** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) Changes in components of the flavouring or colouring system** | | |
| **1. Biological/immunological veterinary medicinal products for oral use for which** | | **S** |

| | | | |
|---|---|---|---|
| | **the colouring or flavouring agent is important for the uptake by target animal species** | | |
| **b)** | **Other excipients** | | |
| | **1. Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the veterinary medicinal product** | | **S** |
| | **2. Change that relates to a biological/immunological product** | | **S** |
| | **3. 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** | | **S** |
| | **4. Change that is supported by a bioequivalence study** | | **S** |
| | **5. Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level** | **1, 2, 3, 4, 5, 6, 7, 8, 9** | **R** |
| **z)** | **Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

| **Documentation** | |
|---|---|
| 1. | Identification method for any new colorant, where relevant. |
| 2. | The results of stability studies that have been carried out under VICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). |
| 3. | Sample of the new product, where applicable. |
| 4. | Either a Ph. Eur. Certificate of Suitability for any new component of animal susceptible to TSE risk or where applicable, documentary evidence that the specific source of the TSE risk material has been previously assessed by the competent authority and shown to comply with the scope of the current *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathies via Human and Veterinary Medicinal Products*. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.<br><br>For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant). |
| 5. | Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate. |
| 6. | Justification for the change/choice of excipients etc. must be given by appropriate development pharmaceutics (including stability aspects and antimicrobial preservation where appropriate). |
| 7. | For solid dosage forms, comparative dissolution profile data of at least two pilot scale batches of the finished product in the new and old composition. For herbal medicinal products, comparative disintegration data may be acceptable. |
| 8. | Justification for not submitting a new bioequivalence study according to the relevant guidance on bioavailability and bioequivalence. |

| | |
|---|---|
| 9. | If 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, or, if not, justification that the excipient does not have pharmacological activity at the dose at which it is administered to the target animal. |

| **F.II.a.4 Change in coating weight of oral dosage forms or change in weight of capsule shells** | | **Documentation to be supplied** | **Timetable** |
|---|---|---|---|
| **a)** | **Gastro-resistant, modified or prolonged release pharmaceutical forms where the coating is a critical factor for the release mechanism** | | **S** |
| **z)** | **Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

| **F.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** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| | | **S** |

| **F.II.a.z Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| | | **R** |

**F.II.b) Manufacture**

| **F.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product** | | **Documentation to be supplied** | **Timetable** |
|---|---|---|---|
| **a)** | **Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/ immunological veterinary medicinal products, or for pharmaceutical forms manufactured by complex manufacturing processes** | | **S** |
| **b)** | **Site which requires an initial or product specific inspection** | | **S** |
| **c)** | **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** | **R** |
| **d)** | **Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile veterianry medicinal products (including those that are aseptically manufactured) excluding biological/ immunological veterinary medicinal products** | **1, 2, 3, 4, 5, 6, 7** | **R** |
| **e)** | **Change in supplier of sterilised primary container components, which are to be used in the aseptic manufacture of veterinary medicinal products** | | **R** |
| **z)** | **Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

| | |
|---|---|
| **Documentation** | |
| 1. | Proof that the proposed site is appropriately authorised for the pharmaceutical form or product concerned, i.e.:<br>For a manufacturing site within the EU/EEA: a copy of the current manufacturing authorisation. A reference to the EudraGMDP database will suffice;<br>For a manufacturing site outside the EU/EEA where an operational GMP mutual recognition agreement (MRA) exists between the country concerned and the EU: a GMP certificate issued within the last 3 years by the relevant competent authority;<br>For a manufacturing site outside the EU/EEA where no such mutual recognition agreement exists: a GMP certificate issued within the last 3 years by an inspection service of one of the Member States of the EU/EEA. A reference to the EudraGMDP database will suffice. |
| 2. | Where relevant, the batch numbers, corresponding batch size and the manufacturing date of batches ($\geq$ 3) used in the validation study should be indicated and the validation data presented, or validation protocol (scheme) to be submitted. |
| 3. | The variation application form should clearly outline the "present" and "proposed" finished product manufacturers as listed in the application form. |
| 4. | Copy of approved release and end-of-shelf life specifications if relevant. |
| 5. | Batch analysis data on one production batch and two pilot-scale batches simulating the production process (or two production batches) and comparative data on the last three batches from the previous site; batch data on the next two production batches should be available on request or reported if outside specifications (with proposed action). |
| 6. | For semisolid and liquid formulations in which the active substance is present in non-dissolved form, appropriate validation data including microscopic imaging of particle size distribution and morphology or any other appropiate imaging technique. |
| 7. | i) If the new manufacturing site uses the active substance as a starting material – A declaration by the Qualified Person (QP) at the site responsible for batch release that the active substance is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union.<br>ii) In addition, if the new manufacturing site is located within the EU/EEA and uses the active substance as a starting material – A declaration by the Qualified Person (QP) of the new manufacturing site that the active substance used is manufactured in accordance with the detailed guidelines on good manufacturing practice for starting materials as adopted by the Union. |
| 8. | If the manufacturing site and the primary packaging site are different, conditions of transport and bulk storage should be specified and validated. |
| Notes | |
| | In case of a change in or a new manufacturing site in a country outside the EU/EEA without an operational GMP mutual recognition agreement with the EU, marketing authorisation holders are advised to consult the relevant competent authorities first before making the submission of the notification and to provide information about any previous EU/EEA inspection in the last 2-3 years and/or any planned EU/EEA inspection(s) including inspection dates, product category inspected, Supervisory Authority and other relevant information. This will facilitate the arrangement for a GMP inspection by an inspection service of one of the Member States if needed.<br><br>**QP Declarations in relation to active substances**<br>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.<br><br>In many cases only one manufacturing authorisation holder is involved and therefore only one declaration will be required. However, when more than one manufacturing authorisation holder is involved rather than provide multiple declarations it may be acceptable to provide a single declaration signed by one QP. This will be accepted provided that: |

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

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

Applicants are reminded that a Qualified Person is at the disposal of a manufacturing authorisation holder according to Article 97 of Regulation (EU) 2019/6 and located in the EU/EEA. Therefore declarations from personnel employed by manufacturers in third countries, including those located within MRA partner countries are not acceptable.

According to Article 88(1) of Regulation (EU) 2019/6, a manufacturing authorisation shall be required in order to carry out any of the following activities: to manufacture veterinary medicinal products even if intended only for export; to engage in any part of the process of manufacturing a veterinary medicinal product or of bringing a veterinary medicinal product to its final state, including engagement in the processing, assembling, packaging and repackaging, labelling and relabelling, storing, sterilising, testing or releasing it for supply as part of that process; or to import veterinary medicinal products. According to Article 88(2) of Regulation (EU) 2019/6, notwithstanding Article 88(1) of Regulation 2019/6, Member States may decide that a manufacturing authorisation shall not be required for preparation, dividing up, changes in packaging or presentation of veterinary medicinal products, where those processes are carried out solely for retail directly to the public in accordance with Articles 103 and 104 of Regulation (EU) 2019/6.

A declaration is not required for blood or blood components. Regulation (EU) 2019/6 does not apply to veterinary medicinal products which have not undergone an industrial process such as, for example, non-processed blood.

| **F.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) Replacement or addition of a site where batch control/testing takes place** | | |
| **1. Replacement or addition of a site where batch control/testing takes place for a biological/immunological veterinary medicinal product and any of the test methods performed at the site is a biological/immunological method** | | **S** |
| **z. Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **b) Replacement or addition of a manufacturer responsible for importation and/or batch release** | | |
| **1. Including batch control/testing for a biological/immunological product and any of the test methods performed at that site is a biological / immunological / immunochemical method** | | **S** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

| **F.II.b.3 Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) Minor change in the manufacturing process** | **1, 2, 3, 4, 5, 6, 7, 8** | **R** |
| **b) Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product** | | **S** |

| | | | |
|---|---|---|---|
| **c)** | **The product is a biological/immunological veterinary medicinal medicinal product and the change requires an assessment of comparability** | | **S** |
| **d)** | **Introduction of a non-standard terminal sterilisation method** | | **S** |
| **e)** | **Introduction or increase in the overage that is used for the active substance** | | **S** |
| **f)** | **Minor change in the manufacturing process of an aqueous oral suspension** | **1, 2, 4, 6, 7, 8** | **R** |
| **g)** | **Move the sterilizing filtration from A/B to C** | | **S** |
| **h)** | **Change in the holding time of an intermediate or bulk product (if applicable)** | | **R** |
| **i)** | **Minor change in the manufacturing process of a sterile finished product after the primary packaging step** | | **R** |
| **z)** | **Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

| | |
|---|---|
| **Documentation** | |
| 1. | Direct comparison of the present process and the new process. |
| 2. | For semi-solid and liquid products in which the active substance is present in non-dissolved form: appropriate validation of the change including microscopic imaging of particles to check for visible changes in morphology; comparative size distribution data by an appropriate method. |
| 3. | For solid dosage forms: dissolution profile data of one representative production batch and comparative data of the last three batches from the previous process; data on the next two full production batches should be available on request or reported if outside specification (with proposed action). For herbal medicinal products, comparative disintegration data may be acceptable. |
| 4. | Justification for not submitting a new bioequivalence study according to the relevant guidance on bioavailability/bioequivalence. |
| 5. | For changes to process parameter(s) that have been considered to have no impact on the quality of the finished product, declaration to this effect reached in the context of the previously approved risk assessment. |
| 6. | Copy of approved release and end-of-shelf life specifications. |
| 7. | Batch analysis data (in a comparative tabulated format) on a minimum of 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 VICH conditions, as appropriate, (with indication of the batch numbers concerned) and relevant stability parameters have been assessed in at least one pilot scale or industrial scale batch and at least three months satisfactory stability data are at the disposal of the applicant at time of notification and that the stability profile is similar to the currently registered situation. Assurance is given that these studies will be finalised and that the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). |

| **F.II.b.4 Change in the batch size (including batch size ranges) of the finished product** | | **Documentation to be supplied** | **Timetable** |
|---|---|---|---|
| **a)** | **The change requires assessment of the comparability of a biological/immunological veterinary medicinal product or the change in batch size requires a new bioequivalence study** | | **S** |

| | | | |
|---|---|---|---|
| **b)** | **The change relates to all other pharmaceutical forms manufactured by complex manufacturing processes** | | **S** |
| **c)** | **More than 10-fold increase compared to the originally approved batch size for immediate release (oral) pharmaceutical forms of biological/immunological products** | **1, 2, 3, 4, 5** | **R** |
| **d)** | **The scale for a biological/immunological medicinal product is increased / decreased without process change (e.g. duplication of line)** | **1, 2, 3, 4, 5** | **R** |
| **z)** | **Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | | |
| 1. | 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). | | |
| 2. | Copy of approved release and end-of-shelf life specifications. | | |
| 3. | Where relevant the batch numbers, corresponding batch size and the manufacturing date of batches (≥3) used in the validation study should be indicated or validation protocol (scheme) be submitted. | | |
| 4. | The validation results should be provided | | |
| 5. | The results of stability studies that have been carried out under VICH conditions, on the relevant stability parameters, on at least one pilot or industrial scale batch, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). For biologicals/immunologicals: a declaration that an assessment of comparability is not required. | | |

| **F.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product** | | **Documentation to be supplied** | **Timetable** |
|---|---|---|---|
| **a)** | **Deletion of an in-process test which may have a significant effect on the overall quality of the finished product** | | **S** |
| **b)** | **Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product** | | **S** |
| **c)** | **Addition or replacement of an in-process test as a result of a safety or quality issue** | **1, 2, 3, 4, 5** | **R** |
| **z)** | **Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | | |
| 1. | Comparative table of current and proposed in-process tests and limits. | | |
| 2. | Details of any new analytical method and validation data, where relevant. | | |
| 3. | Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters. | | |
| 4. | 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. | | |

| | |
|---|---|
| 5. | Justification of the new in-process test and limits. |

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

| **F.II.c.1 Change in the specification parameters and/or limits of an excipient** | | **Documentation to be supplied** | **Timetable** |
|---|---|---|---|
| **a)** | **Change outside the approved specifications limits range** | | **S** |
| **b)** | **Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product** | | **S** |
| **c)** | **Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method, as a result of a safety or quality issue** | **1, 2, 3, 4, 5, 6** | **R** |
| **d)** | **Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the excipient, a change in specification from in-house to a non-official Pharmacopoeia or a Pharmacopoeia of a third country** | **1, 2, 3, 4, 5, 6** | **R** |
| **z)** | **Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

| **Documentation** | |
|---|---|
| 1. | Comparative table of current and proposed specifications. |
| 2. | Details of any new analytical method and validation data, where relevant. |
| 3. | Batch analysis data on two production batches (3 production batches for biological excipients,) of the excipient for all specification parameters. |
| 4. | 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. |
| 5. | Justification for not submitting a new bioequivalence study according to the relevant Guidance on *bioavailability/bioequivalence*, if appropriate. |
| 6. | Justification of the new specification parameter and the limits. |

| **F.II.c.2 Change in test procedure for an excipient** | | **Documentation to be supplied** | **Timetable** |
|---|---|---|---|
| **a)** | **Substantial change to or replacement of a biological/ immunological/ immunochemical test method or a method using a biological reagent** | | **S** |
| **b)** | **Other changes to a test procedure (including replacement or addition)** | **1, 2** | **R** |
| **z)** | **Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

| | |
|---|---|
| **Documentation** | |
| 1. | 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. |

| **F.II.c.3 Change in source of an excipient or reagent with TSE risk** | | **Documentation to be supplied** | **Timetable** |
|---|---|---|---|
| **a)** | **From TSE risk material to vegetable or synthetic origin for excipients or reagents used in the manufacture of a biological / immunological active substance or in a biological / immunological medicinal product** | **1, 2** | **R** |
| **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** | | **S** |
| **z)** | **Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **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. | | |

| **F.II.c.4 Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier) or a novel excipient** | | **Documentation to be supplied** | **Timetable** |
|---|---|---|---|
| **a)** | **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.** | | **S** |
| **b)** | **The excipient is a biological/immunological substance** | | **S** |
| **z)** | **Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

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

| **F.II.d.1 Change in the specification parameters and/or limits of the finished product** | | **Documentation to be supplied** | **Timetable** |
|---|---|---|---|
| **a)** | **Change outside the approved specifications limits range** | | **S** |
| **b)** | **Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product** | | **S** |

| | | |
|---|---|---|
| **c) Addition or replacement (excluding biological or immunological product) of a specification parameter with its corresponding test method as a result of a safety or quality issue** | **1, 2, 3, 4, 5** | **R** |
| **d) Reduction in the testing frequency of an analysis, from routine testing to skip or periodic testing (microbial testing of finished product)** | | **R** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | |
| 1. Comparative table of current and proposed specifications. | | |
| 2. Details of any new analytical method and validation data, where relevant. | | |
| 3. Batch analysis data on two production batches (3 production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters | | |
| 4. 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. | | |
| 5. Justification of the new specification parameter and the limits | | |

| **F.II.d.2 Change in test procedure for the finished product** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) Substantial change to, or replacement of, a biological/ immunological/ immunochemical test method or a method using a biological reagent or replacement of a biological reference preparation not covered by an approved protocol** | | **S** |
| **b) Other changes to a test procedure (including replacement or addition)** | **1, 2** | **R** |
| **c) Replacement of a biological or immunological reference preparation (e.g. reference vaccine batch, reference serum batch) in an immunological/immunochemical test method, which may have a potential significant impact on the quality of the product (e.g. estimate of potency)** | | **S** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | |
| 1. 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. | | |

| **F.II.d.3 Variations related to the introduction of real-time release or parametric release in the manufacture of the finished product** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| | | **S** |

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

| F.II.e.1 Change in immediate packaging of the finished product | Documentation to be supplied | Timetable |
|---|---|---|
| **a) Qualitative and quantitative composition** | | |
| **1. Semi-solid and non-sterile liquid pharmaceutical forms** | **1, 2, 3, 4** | **R** |
| **2. Sterile medicinal products and biological/ immunological medicinal products.** | | **S** |
| **3. The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life.** | | **S** |
| **b) Change in type of container or addition of a new container*** | | |
| **1. Solid, semi-solid and non-sterile liquid pharmaceutical forms** | **1, 2, 3, 4, 5** | **R** |
| **2. Sterile medicinal products and biological/ immunological medicinal products** | | **S** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | |
| 1. Appropriate data on the new packaging (comparative data on permeability e.g. for $O_2$, $CO_2$ moisture). | | |
| 2. 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. | | |
| 3. The results of stability studies that have been carried out under VICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of 3 months, and an assurance is given that these studies will be finalised, and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action). | | |
| 4. Comparative table of the current and proposed immediate packaging specifications, if applicable. | | |
| 5. Samples of the new container/closure where applicable. | | |
| *Note: Marketing authorisation holders are reminded that any change which results in a "new pharmaceutical form" is classified as a variation under chapter I of this annex. | | |

| F.II.e.2 Change in the specification parameters and/or limits of the immediate packaging of the finished product | Documentation to be supplied | Timetable |
|---|---|---|
| **a) Addition or replacement of a specification parameter as a result of a safety or quality issue** | **1, 2, 3, 4** | **R** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

| | |
|---|---|
| **Documentation** | |
| 1. | Comparative table of current and proposed specifications. |
| 2. | Details of any new analytical method and validation data, where relevant. |
| 3. | Batch analysis data on two batches of the immediate packaging for all specification parameters. |
| 4. | Justification of the new specification parameter and the limits. |

| **F.II.e.3 Change in test procedure for the immediate packaging of the finished product** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

| **F.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging)** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) 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** | | **S** |
| **b) Sterile medicinal products** | **1, 2, 3, 4** | **R** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | |
| 1. Description, detailed drawing and composition of the container or closure material. | | |
| 2. Samples of the new container/closure where applicable. | | |
| 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 VICH 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 submission, 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). | | |

| **F.II.e.5 Change in pack size of the finished product** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) Change in the number of units (e.g. tablets, ampoules, etc.) in a pack outside the range of the currently approved pack sizes** | **1, 2** | **R** |
| **b) Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/immunological medicinal products.** | | **S** |

| | | |
|---|---|---|
| **c) Change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) products** | **1, 2** | **R** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | |
| 1. Justification for the new pack-size, showing that the new size is consistent with the dosage regimen and duration of treatment as approved in the summary of product characteristics | | |
| 2. 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 F.II.e.5.b) and c), marketing authorisation holders are reminded that any change to the 'strength' of the medicinal product is classified as a variation under chapter I of this annex. | | |

| **F.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))** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

| **F.II.e.7 Change in supplier of packaging components or devices (when mentioned in the dossier)** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) Any change to suppliers of spacer devices for metered dose inhalers** | | **S** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

**F.II.f) Stability**

| **F.II.f.1 Change in the shelf-life or storage conditions of the finished product** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) Extension of the shelf life of the finished product** | | |
| **1. As packaged for sale (supported by real time data)** | **1, 2** | **R** |
| **2. After first opening (supported by real time data)** | **1, 2** | **R** |
| **3. After dilution or reconstitution (supported by real time data)** | **1, 2** | **R** |
| **4. Extension of the shelf-life based on extrapolation of stability data not in accordance with VICH guidelines*** | | **S** |
| **5. Extension of the shelf-life of a biological/immunological medicinal product** | **1, 2** | **R** |

| | | | |
|---|---|---|---|
| | **in accordance with an approved stability protocol.** | | |
| **b)** | **Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol** | | **S** |
| **c)** | **Change in storage conditions of the finished product or the diluted/reconstituted product** | **1, 2** | **R** |
| **z)** | **Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | | |
| 1. | 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.<br>[1]Pilot scale batches can be accepted with a commitment to verify the shelf life on production scale batches. | | |
| 2. | 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 | | |

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

| **F.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product, concerning:** | | **Documentation to be supplied** | **Timetable** |
|---|---|---|---|
| **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** | **S** |
| **b)** | **Test procedures for excipients/intermediates and/or the finished product.** | **1, 2** | **S** |
| **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. | | |

| **F.II.g.2 Changes to or introduction of a post approval change management protocol related to the finished product** | | **Documentation to be supplied** | **Timetable** |
|---|---|---|---|
| **a)** | **Introduction of a post approval change management protocol related to the finished product** | **1, 2** | **S** |

| | | | |
|---|---|---|---|
| **b)** | **Changes to an approved change management protocol** | | |
| | **1. Major changes to an approved change management protocol** | | **S** |
| | **2. Minor changes to an approved change management protocol that do not change the strategy defined in the protocol** | **3** | **R** |
| **c)** | **Implementation of changes foreseen in an approved change management protocol** | | |
| | **1. The implementation of the change requires further supportive data** | **4, 5, 6** | **R** |
| | **2. Implementation of a change for a biological/immunological product** | **4, 5, 6, 7** | **R** |

| | |
|---|---|
| **Documentation** | |
| 1. | Detailed description for the proposed change. |
| 2. | Change management protocol related to the finished product. |
| 3. | Declaration that any change should be within the range of currently approved limits. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products. |
| 4. | Reference to the approved change management protocol. |
| 5. | 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. |
| 6. | Results of the studies performed in accordance with the approved change management protocol. |
| 7. | Copy of approved specifications of the finished product. |

| **F.II.g.z Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| | | **R** |

### *F.III CEP/TSE/MONOGRAPHS*

| **F.III.1 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability:**<br><br>**For an active substance**<br><br>**For a starting material/reagent/intermediate used in the manufacturing process of the active substance**<br><br>**For an excipient** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.** | | |
| **1. New certificate for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free** | **1, 2, 3, 4, 5** | **R** |

| | | | |
|---|---|---|---|
| | **z. Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **b)** | **European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient** | | |
| | **1. New/updated certificate from an already-approved/new manufacturer using materials of human or animal origin for which an assessment of the risk with respect to potential contamination with adventitious agents is required** | | **S** |
| | **z. Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

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

| **F.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State** | | **Documentation to be supplied** | **Timetable** |
|---|---|---|---|
| **z)** | **Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

***F.IV DEVICES***

| **F.IV.1 Change of a measuring or administration device** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) Addition or replacement of a device which is not an integrated part of the primary packaging** | | |
| **1. Device without CE marking** | **1, 2, 3** | **R** |
| **2. Spacer device for metered dose inhalers or other device which may have a significant impact on the delivery of the active substance in the product (e.g. nebuliser)** | | **S** |
| **b) Addition or replacement of a device which is an integrated part of the primary packaging*** | | **S** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | |
| 1. Description, detailed drawing and composition of the device material and supplier where appropriate. | | |
| 2. Data to demonstrate accuracy, precision and compatibility of the device. | | |
| 3. Samples of the new device where applicable. | | |
| *Note: Marketing authorisation holders are reminded that any change which results in a "new pharmaceutical form" is classified as a variation under chapter I of this annex. | | |

| **F.IV.2 Change in specification parameters and/or limits of a measuring or administration device** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) Widening of the approved specifications limits, which has a significant effect on the overall quality of the device** | | **S** |
| **b) Deletion of a specification parameter that has a significant effect on the overall quality of the device** | | **S** |
| **c) Addition of a specification parameter as a result of a safety or quality issue** | **1, 2, 3, 4** | **R** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **Documentation** | | |
| 1. Comparative table of current and proposed specifications. | | |
| 2. Details of any new analytical method and summary of validation data. | | |
| 3. Batch analysis data on two production batches for all tests in the new specification. | | |
| 4. Justification for the new specification parameter and the limits | | |

| **F.IV.3 Change in test procedure of a measuring or administration device** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

## *F.V. CHANGES TO A MARKETING AUTHORISATION RESULTING FROM OTHER REGULATORY PROCEDURES*

### F.V.a) VAMF/PTMF

| **F.V.a.1 Inclusion of a new, updated or amended Vaccine Antigen Master File in the marketing authorisation dossier of a medicinal product. (VAMF 2nd step procedure)** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) First-time inclusion of a new Vaccine Antigen Master File** | | **S** |
| **b) Inclusion of an updated/amended Vaccine Antigen Master File, when changes affect the properties of the finished product** | **1, 2, 3, 4** | **S** |
| **Documentation** | | |
| 1. Declaration that the VAMF Certificate and Evaluation Report are fully applicable for the authorised product, VAMF holder has submitted the VAMF Certificate, Evaluation report and VAMF dossier to the MAH (where the MAH is different to the VAMF holder), the VAMF Certificate and Evaluation Report replace the previous VAMF documentation for this Marketing Authorisation. | | |
| 2. VAMF Certificate and Evaluation Report. | | |
| 3. An expert statement outlining all the changes introduced with the certified VAMF and evaluating their potential impact on the finished products including product specific risk assessments. | | |
| 4. The variation application form should clearly outline the "present" and "proposed" VAMF EMA Certificate (code number) in the MA dossier. When applicable, the variation application form should clearly list also all the other VAMFs to which the medicinal product refers even if they are not the subject of the application. | | |

| **F.V.a.2 Inclusion of a new, updated or amended Platform Technology Master File in the marketing authorisation dossier of a medicinal product. (PTMF 2nd step procedure)** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) First-time inclusion of a new PTMF** | | **S** |
| **b) Inclusion of an updated/amended PTMF when changes affect the finished product** | | **S** |

### F.V.b) Harmonisation of the quality dossier

| **F.V.b.1 Harmonisation of the quality dossier** | **Documentation to be supplied** | **Timetable** |
|---|---|---|
| **a) Harmonisation of the quality dossier after a Union interest referral procedure when the quality dossier was not part of the referral** | | **S** |
| **b) Harmonisation of the quality dossier after a SPC harmonisation procedure** | | **S** |
| **c) Harmonisation of the quality dossier for the same purely national products and/or the same products approved in MR/DC procedures which are owned by the same MAH not participating in a former union interest referral procedure or SPC harmonisation procedure** | | **S** |

## CHAPTER G. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES

| G.I.1 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union interest referral procedure according to Article 83 of Regulation (EU) 2019/6 | Documentation to be supplied | Timetable |
|---|---|---|
| **a) The medicinal product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure and no new additional data is required to be submitted by the MAH** | **1, 2** | **R** |
| **b) The medicinal product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure with new additional data submitted by the MAH** | **1** | **S** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |
| **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. | | |

| G.I.2 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid medicinal product following assessment of the same change for the reference product | Documentation to be supplied | Timetable |
|---|---|---|
| **a) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH (e.g. comparability)** | | **S** |
| **b) Harmonisation of the generic/hybrid product according to article 71(1) after SPC harmonisation of the reference product** | | **S** |
| **z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance** | | **R** |

| G.I.3 Change(s) in the SPC, labelling or package leaflet intended to implement the outcome of a procedure or recommendations from the competent authority or the Agency concerning risk management measures in pharmacovigilance related to veterinary medicinal products | Documentation to be supplied | Timetable |
|---|---|---|
| **a) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH** | **1** | **S** |
| **b) Implementation of wording agreed by the competent authority that require additional minor assessment, e.g. translations are not yet agreed upon** | **1** | **R** |

| Documentation |
|---|
| 1. Attached to the cover letter of the variation application: a reference to the agreement/assessment of the competent authority. |

| G.I.4 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet due to new quality, preclinical, clinical or pharmacovigilance data. | Documentation to be supplied | Timetable |
|---|---|---|
| | | **S** |
| Note: This variation does not apply when the new data has been submitted under variation G.I.9 In such cases, the change(s) in the SPC, labelling and/or package leaflet is covered by the scope of variation G.I.9. | | |

| G.I.5 Product Information update, for a medicinal product containing more than one active substance, in order to include significant changes. | Documentation to be supplied | Timetable |
|---|---|---|
| **a) Those changes were already assessed by a EU competent authority for a medicinal product containing one of the active substances, and the same wording will be used for the combination product** | **1** | **S** |
| **Documentation** | | |
| 1. Attached to the cover letter of the variation application: a reference to the procedure where the wording for one of the active substances was approved. | | |

| G.I.6 Change in the legal status of a medicinal product for centrally authorised products. | Documentation to be supplied | Timetable |
|---|---|---|
| **a) For generic/hybrid/biosimilar medicinal products following an approved legal status change of the reference medicinal product** | **1** | **R** |
| **b) All other legal status changes** | | **S** |
| **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) | | |
| Note: For Nationally Authorised Products approved via MRP/DCP the change in legal status is to be handled at national level (not via MRP variation). | | |

| G.I.7 Change(s) to therapeutic indication(s) | Documentation to be supplied | Timetable |
|---|---|---|
| **a) Addition of a new therapeutic indication or modification of an approved one** | | **E** |
| **b) Deletion of a therapeutic indication** | | **R** |
| Note: Where the change takes place in the context of the implementation of the outcome of a referral procedure, or -for a generic/hybrid product- when the same change has been done for the reference product, variations G.I.1 and G.I.2 apply, respectively. | | |

| G.I.8 Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan | Documentation to be supplied | Timetable |
|---|---|---|
| **a) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment by the competent authority is required*** | | **S** |
| **b) Introduction of a risk management plan** | | **S** |
| *Note: This variation covers the situation where the only change introduced concerns the conditions and/or obligations of the marketing authorisation, including the risk management plan and the conditions and/or obligations of marketing authorisations under exceptional circumstances. | | |

| G.I.9 Other variations not specifically covered elsewhere in chapter G which involve the submission of studies to the competent authority, including additional clinical and non-clinical studies, including BE-studies | Documentation to be supplied | Timetable |
|---|---|---|
| | | **E** |
| Note: In cases where the assessment by the competent authority of the data submitted leads to a change of the Summary of Product Characteristics, Labelling or Package Leaflet, the relevant amendment to the Summary of Product Characteristics, Labelling or Package Leaflet is covered by the variation.<br>This variation does not apply to variations that can be considered as z-variation elsewhere in chapter G. | | |

| G.I.10 Variations concerning a change to or addition of a non-food producing target species. | Documentation to be supplied | Timetable |
|---|---|---|
| | | **E** |

| G.I.11 Deletion of a food producing or non-food producing target species. | Documentation to be supplied | Timetable |
|---|---|---|
| **a) Deletion as a result of a safety issue** | | **S** |
| **b) Deletion not resulting from a safety issue** | **1** | **R** |
| **Documentation** | | |
| 1. Justification for the deletion of the target species | | |

| G.I.12 Changes to the withdrawal period for a veterinary medicinal product | Documentation to be supplied | Timetable |
|---|---|---|
| | | **S** |

| G.I.13 Variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for a veterinary vaccine based on a multistrain dossier. | Documentation to be supplied | Timetable |
|---|---|---|
| | | **E** |

| G.I.14 Variations concerning the replacement of a strain for a veterinary vaccine against equine influenza. | Documentation to be supplied | Timetable |
|---|---|---|
| | | E |

| G.I.15 Changes to the labelling or the package leaflet which are not connected with the summary of product characteristics. | Documentation to be supplied | Timetable |
|---|---|---|
| z) Other changes under this code level, e.g. variations outlined in section 6 and 7 of this guidance | | R |

| G.I.16 Clarification of the temperature of use in section 4.9 of the SPC and section 8 of the PL to ensure the correct handling of the veterinary medicinal product | Documentation to be supplied | Timetable |
|---|---|---|
| | | R |

| G.I.17 Changes in relation to MR/SR procedures | Documentation to be supplied | Timetable |
|---|---|---|
| a) Update of the dossier in preparation of a SRP/MRP/duplicate application in order to conform to the current legislation | | S |
| b) Adaptation of the Product Information for the original Concerned Member States after a SRP* | | R |
| *Note: This variation should only be submitted to the original Concerned Member States. | | |

| G.I.18 One-off alignment of the product information with version 9.0* of the QRD templates i.e. major update of the QRD templates in accordance with Regulation (EU) 2019/6, for veterinary medicinal products authorised in accordance with Directive 2001/82/EC or Regulation (EC) No 726/2004 | Documentation to be supplied | Timetable |
|---|---|---|
| | | S |
| *Version 9.0, or the latest version of the QRD templates that are in effect at the time that this one-off variation is submitted.<br><br>Note: In accordance with Regulation (EU) 2022/839, this variation should be submitted so that the variation is finalised and implemented on the printed labelling and package leaflet before 29 January 2027. Grouping with other variations in chapter G affecting the product information texts for the same product is recommended. | | |

| G.I.19 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet to implement the outcome of the MAH's signal management process according to Article 81(2) of Regulation (EU) 2019/6 | Documentation to be supplied | Timetable |
|---|---|---|
| | **1, 2** | **R** |
| **Documentation** | | |
| 1. A confirmation that the related signal has been submitted in the Union Pharmacovigilance database, in the module for Veterinary Signal Management (VSM) submissions (IRIS). The procedure number for the VSM submission in IRIS (e.g., EMA/VS/XXXXXXXXXX) will suffice. | | |
| 2. The veterinary signal assessment report for MAHs in line with the relevant template available on the EMA website, and any references or supporting documentation. | | |
| Note: This variation covers the situations where the new data consists mostly of data from the Union pharmacovigilance database. For cases where studies or extensive published literature references are to be submitted, or where the recommendations to update the product information concern several safety-related or lengthy sections, or where other risk minimisation measures are involved, variation G.I.4 applies. Further guidance is available in the template for the veterinary signal assessment report available on the EMA website. | | |

## CHAPTER H. VAMF/PTMF CHANGES 1st STEP

Codes for specific VAMF/PTMF 1st step variations may be added in a future revision of this guidance. In general, the respective F-codes are to be used for the 1st step of the VAMF/PTMF certification updates. Implementation on product-level are to be submitted under the F.V.a-codes, as required.

## CHAPTER I. CHANGES OF ACTIVE SUBSTANCE(S), STRENGTH, PHARMACEUTICAL FORM, ROUTE OF ADMINISTRATION OR FOOD PRODUCING TARGET SPECIES

| I.I.1 Changes to the active substance(s) | | Documentation to be supplied | Timetable |
|---|---|---|---|
| **a)** | **Replacement of a chemical active substance by a different salt/ester complex/derivative, with the same therapeutic moiety, where the efficacy/safety characteristics are not significantly different** | | **E** |
| **b)** | **Replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer), where the efficacy/safety characteristics are not significantly different** | | **E** |
| **c)** | **Replacement of a biological active substance with one of a slightly different molecular structure where the efficacy/safety characteristics are not significantly different, with the exception of the changes mentioned in G.I.13 and G.I.14** | | **E** |
| **d)** | **Modification of the vector used to produce the antigen or the source material, including a new master cell bank from a different source, where the efficacy/safety characteristics are not significantly different** | | **E** |
| **e)** | **A new ligand or coupling mechanism for a radiopharmaceutical, where the efficacy/safety characteristics are not significantly different** | | **E** |
| **f)** | **Change to the extraction solvent or the ratio of herbal drug to herbal drug preparation where the efficacy/safety characteristics are not significantly different** | | **E** |

| I.II.1 Changes to strength, pharmaceutical form and route of administration | | Documentation to be supplied | Timetable |
|---|---|---|---|
| **a)** | **Change of bioavailability** | | **E** |
| **b)** | **Change of pharmacokinetics e.g. change in rate of release** | | **E** |
| **c)** | **Change or addition of a new strength/potency (1)** | | **E** |
| **d)** | **Change or addition of a new pharmaceutical form** | | **E** |
| **e)** | **Change or addition of a new route of administration (2)** | | **E** |

Notes:

Including decrease in vial size for a multi-dose vaccine. Consequential changes to be included in the scope of the variation: reduction in diluent volume, reduction in dose volume, increasing antigen & excipient concentration per 1 ml, change in specification of in-process and final control (different no. CFU/ml).

For parenteral administration, it is necessary to distinguish between intra-arterial, intra-venous, intramuscular, subcutaneous and other routes. For administration to poultry, respiratory, oral and ocular (nebulisation) routes used for vaccination are considered to be equivalent routes of administration.

| I.III.1 Other changes specific to veterinary medicinal products to be administered to food-producing animals | Documentation to be supplied | Timetable |
|---|---|---|
| **a) Change or addition of target species** | | **E** |