Medicines Control Authority of Zimbabwe

MCAZ/EVR/GL-07

GUIDELINES ON POST-AUTHORISATION VARIATIONS FOR VETERINARY MEDICINAL PRODUCTS

EFFECTIVE DATE: 20/2/2024

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Authorised for use by: Director-General	..... Signature	20/2/2024 ..... Date

Contents

ABBREVIATIONS

ASMF – Active Substance Master File

CEP – Certificate of Suitability of the European Pharmacopoeia

CMP – Change Management Protocol

DER – Drug Extract Ratio

EU – European Union

MCAZ – Medicines Control Authority of Zimbabwe

Ph.Eur – European Pharmacopoeia

PSMF - Pharmacovigilance System Master File

PTMF - Platform Technology Master File

QP – Qualified Person

QPPV - Qualified Person for Pharmacovigilance

SPC – Summary of Product Characteristics

TSE - Transmissible Spongiform Encephalopathy

VAMF - Vaccine Antigen Master File

VICH - International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products

VMP – Veterinary Medicinal Product

1.0 APPLICATION

These guidelines apply to all changes to the terms of registration/marketing authorization. These guidelines provide the necessary information that must be submitted by all applicants to the Medicines Control Authority of Zimbabwe (MCAZ) when submitting applications for variations to registered veterinary medicinal products (VMPs).

2.0 PURPOSE

This guidance document is applicable only to Active Pharmaceutical Ingredients (APIs) and excipients manufactured by chemical synthesis or semisynthetic processes and Finished Pharmaceutical Products (FPPs) containing such APIs and excipients. Variations to a biological API and/or biological excipient, or biological finished products are assessed as major changes. The guidelines are also applicable to variations for all complementary medicines.

These guidelines have been prepared taking into consideration the need for global harmonization and to facilitate timeous and efficient processing of variations not requiring assessment and variations requiring assessment.

3.0 BACKGROUND / INTRODUCTION

This variation guideline provides the necessary information that must be submitted by all applicants to the Medicines Control Authority of Zimbabwe (MCAZ) for all VMPs.

These guidelines were adapted from the Commission Implementing Regulation (EU) 2021/17 of 8 January 2021 based on Article 60(1) of the Regulation (EU) 2019/6 and the Guidance on the details of the classification of variations requiring assessment according to Article 62 of Regulation (EU) 2019/6 for veterinary medicinal products.

4.0 DEFINITIONS

4.1 **Applicant** means the person by, or on whose behalf, an application for registration is made.

4.2 **CE marking** means an acronym for the French “Conformite Europeenne” which certifies that a product has met EU health, safety, and environmental requirements, which ensure consumer safety.

4.3 **Complementary medicine** means any substance or mixture of substances which is used, or is manufactured, sold or represented as suitable for use, in- (a) the mitigation or prevention of disease or abnormal physical mental state or the symptoms thereof in animals; (b) restoring, correcting or

modifying any physical, mental or organic function in animals; which originates from a plant, mineral, animal or insect and includes substances generally referred to as Aromatherapeutic Substances, Ayurvedic Medicines, Energy Substances or Medicines, Homeopathic Remedies, Nutritional Substance in pharmaceutical form. Traditional Chinese Medicines, Traditional Dutch Remedies, Unanni Tibb Medicines, Western Herbal Medicines and such other medicines or remedies as may be approved by the Authority;

4.4 **Veterinary Medicinal Product** means any preparation for veterinary use that is intended to modify or explore physiological systems or pathological states for the benefit of the recipient.

4.5 **Variation Requiring Assessment** means any variation that is not listed under section 5.3 table 1 of these guidelines shall follow procedure for an application for variation requiring assessment.

4.6 **Variations Not Requiring Assessment** means any variation that is listed under section 5.3 table 1 of these guidelines shall follow the procedure laid down in that section.

4.7 **VICH region** includes the regions EU, Japan and USA.

4.8 **Timelines for variation procedures** means that variations requiring assessment may have different levels of complexity and considering the timeframes within which variations requiring assessment are to be completed, the following shall apply:

4.9 "**R**" for Reduced timeline means an assessment report and/or decision shall be prepared within 3 months of receipt of a valid application of a variation;

4.10 "**S**" for Standard timeline means an assessment report and/or decision shall be prepared within 6 months of receipt of a valid application of a variation;

4.11 "**E**" for Extended timeline means an assessment report and/or decision shall be prepared within 12 months of receipt of a valid application of a variation.

5.0 GUIDELINES

5.1 Procedure for Approval of Variations

5.1.1 The applicant submits an application in the appropriate format accompanied by the appropriate forms and fees.

5.1.2 MCAZ evaluators conduct screening of application for completeness and confirmation of type of variation and fee payable. Incomplete applications will then be rejected at this stage.

5.1.3 The application is assessed by MCAZ evaluators and matter considered at a meeting of the MCAZ Committee where a decision on the application is made.

5.1.4 The applicant is notified of the Authority's decision and any applicable conditions or request for more information.

5.2 Fees

Applicable fees are defined in the MCAZ fee schedule. Note that the MCAZ reserves to determine the correct interpretation of the fee payable based on the published schedule. Please note that relevant variation application fees apply to all variations. Any submission not accompanied by the relevant application fee will not be considered as an application.

5.3 Variations Not Requiring Assessment

Variations which satisfy the requirements applicable to them as set out Table 1, shall not require assessment. Requirements, including conditions and documentation, shall be provided by the applicant to keep the product dossier updated. Fulfilment of the requirements will form a basis for rejection or approval of the variation.

Table 1: List of variations that do not require assessment to be implemented

Variation		**Requirements** The requirements indicated in the line for the main section are valid for each sub-section of the given section. Any additional requirement specified in the sub-section should be read together with the requirements indicated in the main section.	
Number		**Conditions**	**Documents to be provided**
A	**Administrative changes**		
1	**Change in the name or address or contact details of:**		
a)	the applicant or principal	The applicant or principal shall remain the same legal entity.	Updated relevant pages of the MC8 form
b)	- a manufacturer or supplier of the active substance, starting	The manufacturing or quality control site and all	

	material, reagent or intermediate used in the - manufacture of the active substance or a quality control testing site (where specified in the dossier) where no European Pharmacopoeia (Ph. Eur.) Certificate of Suitability (CEP) is part of the approved dossier.	manufacturing operations shall remain the same.	
c)	- an active substance master file (ASMF) holder	The manufacturing site and all manufacturing operations shall remain the same.	Updated 'letter of access' to the Active Substance Master File.
d)	- a manufacturer of an excipient (where specified in the dossier)	The manufacturing site and all manufacturing operations shall remain the same.	
e)	- a manufacturer or importer of the finished product (including batch release or quality control testing sites)	The manufacturing site and all manufacturing operations shall remain the same.	Updated relevant pages of the MC8 form; Revised label and package insert
2	Change in the (invented) name of the veterinary medicinal product	The acceptability review of the new name by the Authority, as applicable, shall be finalised and is positive.	Updated relevant pages of the MC8 form; Revised label and package insert
3	Change in name of the active substance or of an excipient	The substance shall remain the same.	
B	**Changes to the quality part of the dossier**		
1	Change in the name or address or contact details of a supplier of a packaging component or of a	The manufacturing site shall remain the same.	

	device of the finished product (where mentioned in the dossier)		
2	Change in the nomenclature of the material for immediate packaging of the finished product	The change shall only be introduced following amendment to the name of the container in the standard terms database	
3	**Deletion of:**		Amendment of the relevant section(s) of the dossier.
a)	- a manufacturing site for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material for an active substance, reagent or excipient (when mentioned in the dossier)	The deletion shall not be due to critical deficiencies concerning manufacturing. There shall at least remain one site or manufacturer, as previously authorised, performing the same function as the one(s) concerned by the deletion. There shall at least remain one site or manufacturer responsible for batch release	
b)	- a manufacturing process for the active substance or the finished product, including an intermediate used in the manufacture of the finished product when an alternative is already approved	The finished product, active substance, intermediates or in-process materials used in the manufacture of the finished product shall still conform to the approved specifications. The deletion shall not be due to critical deficiencies concerning manufacturing.	

c)	- a non-significant in-process test during the manufacture of the active substance (e.g. deletion of an obsolete in-process test)	The change shall not relate to a commitment or to an unexpected event during manufacture. The change shall not concern a critical in-process test and shall not have the potential to affect the identity, quality, purity, potency or physical characteristics of the active substance, starting material, intermediate or reagent used in the manufacturing process of the active substance.	Comparative table of former and new in-process test.
d)	- a non-significant specification parameter (e.g. deletion of an obsolete parameter) of - an active substance; - a starting material; - an intermediate or reagent used in the manufacturing process of the active substance	The change shall not relate to a commitment or to an unexpected event during manufacture. The change shall not concern a critical specification parameter or have the potential to affect the identity, quality, purity, potency or physical characteristics of the active substance, starting material, intermediate or reagent used in the manufacturing process of the active substance.	Comparative table of former and new specifications.
e)	- a test procedure - for the active substance or a starting material, reagent or intermediate of the active substance;	An alternative test procedure shall already be authorised by the Authority and this test procedure has not been added through a variation procedure not requiring assessment.	

	- for the immediate packaging of the active substance; - for an excipient or the finished product; - for the immediate packaging of the finished product		
f)	- one of the authorised bulk or final containers (including packaging of an active substance) or immediate packaging of the finished product that does not lead to the complete deletion of a strength or pharmaceutical form	Where applicable, the remaining product presentations shall be adequate for the dosing instructions and treatment duration as defined in the summary of product characteristics.	
g)	- a non-significant specification parameter (e.g. deletion of an obsolete parameter) in the specification parameters or limits of the immediate packaging of the active substance or the finished product	The change shall not relate to a commitment or to an unexpected event during manufacture of the immediate packaging material and storage of the active substance or the finished product. The change shall not concern a critical parameter or have the potential to affect the identity or quality of the immediate packaging.	Comparative table of former and new specifications.
h)	- an approved change management protocol related to the active substance or the finished product	The change shall not be the result of an unexpected event or an out of specification result during the implementation of the change(s) described in the protocol.	
i)	- a component or components of the	The change shall not be applicable to a biological or immunological	

	flavouring or colouring system	medicinal product. The change shall not have the potential to affect the identity, strength, quality, purity, potency, safety or effectiveness of the finished product.	
j)	- a solvent or diluent container from the pack	The pharmaceutical form shall remain unchanged. There shall be appropriate alternative means to obtain the solvent or diluent as required for the safe and effective use.	
k)	- a non-significant in-process test (e.g. deletion of an obsolete test) during the manufacture of the finished product	The change shall not relate to a commitment or to an unexpected event during manufacture. The change shall not concern a critical parameter or have the potential to affect the identity, quality, purity, potency or physical characteristics of the finished product or starting material, intermediate or reagent used in the manufacturing process of the finished product.	Comparative table of former and new in-process tests and limits.
l)	details on testing frequency by the finished product manufacturer of an excipient or an active substance or of packaging material for the immediate packaging of an active substance or the finished product, when mentioned in the dossier		
m)	- a non-significant specification parameter (e.g. deletion of an obsolete parameter) in the specification parameters or limits of an excipient	The change shall not relate to a commitment or to an unexpected event during manufacture. The change shall not concern	Comparative table of former and new specification parameters or limits.

		a critical parameter or have the potential to affect the identity, quality, purity, potency or physical characteristics of the excipient.	
n)	a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material) in the specification parameters or limits of the finished product	The change shall not relate to a commitment or to an unexpected event during manufacture. The change shall not concern a critical parameter or have the potential to affect the identity, strength, quality, purity, potency or physical characteristics of the finished product.	Comparative table of former and new specification parameters or limits.
o)	- a measuring or administration device	The change shall not affect the delivery, use or safety of the finished product.	
p)	- a non-significant specification parameter (e.g. deletion of an obsolete parameter) of a measuring or administration device	The change shall not relate to a commitment or to an unexpected event during manufacture. The change shall not concern a critical parameter or have the potential to affect the identity or quality of the measuring or administration device.	Comparative table of former and new specifications.
q)	- a test procedure of a measuring or administration device	An alternative test procedure shall already be authorised by the Authority.	
r)	- pack size(s) of the finished product	The remaining pack-sizes shall be consistent with the posology and treatment duration as	

		approved in the summary of product characteristics.	
s)	- a supplier of packaging components or devices (when mentioned in the dossier)	The change shall not include the deletion of a packaging component(s) or a device(s).	
t)	- a Ph. Eur. CEP - for an active substance; - for a starting material, reagent or intermediate used in the manufacturing process of the active substance; - for an excipient	At least one manufacturer for the same substance shall remain in the dossier.	
u)	- a Ph. Eur. Transmissible Spongiform Encephalopathy (TSE) CEP - for an active substance; - for a starting material, reagent or intermediate of an active substance; - for an excipient	At least one manufacturer for the same substance shall remain in the dossier.	
4	**Changes to the production process or the storage of active substance where no Ph. Eur. CEP is part of the approved dossier of an active substance (including starting material, reagent or intermediate)**	**For starting materials and reagents the specifications (including in-process controls, methods of analysis of all materials), shall be identical to those already approved. For intermediates and active substance(s) the specifications (including in process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis shall be identical to those already approved.**	
a)	change in the manufacturer of the active substance (including relevant quality control testing sites)	The change shall not be applicable to a sterile active substance or a biological or	The Amendment of the relevant section (s) of the dossier

		immunological substance. The change shall not be applicable to a herbal substance or a herbal preparation in a herbal medicinal product. The new manufacturer shall be part of the same pharmaceutical group as the currently approved manufacturer. The change shall not have the potential to affect the identity, quality, purity, potency or physical characteristics of the active substance, starting material, intermediate or reagent used in the manufacturing process of the active substance.	shall be provided, as appropriate, for: - TSE data, - batch data, - qualified person (QP) declaration and - confirmation of GMP compliance.
b)	- changes to quality control testing arrangements for the active substance: replacement or addition of a site where batch control or testing of the active substance takes place	The change shall not be applicable to a sterile active substance or a biological or immunological substance. Method transfer from the former to the new site shall have been successfully completed.	
c)	- introduction of a new site of micronisation for the manufacturer of the active substance (including relevant quality control testing sites)	The change shall not be applicable to a sterile active substance or a biological or immunological substance. The change shall not provoke an adverse change in physico-chemical properties. The particle size specification for the active substance and the corresponding analytical method shall remain the same.	Amendment of the relevant section(s) of the dossier for QP declaration and comparative batch data from the former and new site, as appropriate.
d)	- new storage site of Master Cell Bank or Working Cell Banks for	No change shall be made to the storage conditions,	

	the manufacturer of a starting material, reagent or intermediate used in the manufacturing process of the active substance or the active substance itself	the shelf-life and the specifications.	
5	Reduction of re-test period or storage period where no Ph. Eur. CEP covering the retest period is part of the approved dossier	The change shall not be the result of unexpected events arising during manufacture or because of stability concerns.	Amendment of the relevant section(s) of the dossier including specifications and stability confirmation, as appropriate.
6	Change to more restrictive storage conditions:	The change shall not be the result of unexpected events arising during manufacture or because of stability concerns.	Amendment of the relevant section(s) of the dossier including specifications and stability confirmation, as appropriate.
a)	- of the reference standard (when mentioned in the dossier)		
b)	- of the active substance		
7	Change to an approved stability protocol of an active substance (including starting material, reagent or intermediate)	The change shall not be the result of unexpected events arising during manufacture or because of stability concerns. The change shall not have the potential to affect the identity, strength, quality, purity, potency or physical characteristics of the active substance.	Amendment of the relevant section(s) of the dossier including results of appropriate real time stability studies.
8	Implementation of changes foreseen in an approved change management protocol (CMP) for the active substance	The change shall be in accordance with the approved CMP and the results of studies performed indicate that the predefined acceptance criteria specified in the protocol are met. The implementation of the change shall require no further supportive data to the CMP.	Amendment of the relevant section(s) of the dossier.

9	Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance	The change shall not be applicable to a sterile active substance or a biological or immunological substance. The change shall not adversely affect the reproducibility of the process. The change shall not be the result of unexpected events arising during manufacture or because of stability concerns. Changes to the manufacturing methods shall only be those necessitated by scale-up or downscaling, e.g. use of different-sized equipment. The batches tested shall have the proposed batch size.	Amendment of the relevant section(s) of the dossier including batch data, as appropriate.
a)	- up to 10-fold increase compared to the originally approved batch size	The active substance and all intermediates, reagents, catalysts or solvents shall still conform to the approved specifications.	
b)	- downscaling down to 10-fold		
c)	- more than 10-fold increase compared to the originally approved batch size	The intermediates, reagents, catalysts or solvents used in the process shall remain the same. The active substance and all intermediates, reagents, catalysts or solvents shall still conform to the approved specifications. The change shall not provoke an adverse change in qualitative and quantitative impurity profile, potency or in physico-chemical properties of the active substance. The change shall not refer to the	

		restricted part of an ASMF.	
10	Change to in-process tests or limits applied during the manufacture of the active substance	The change shall not be a consequence of any commitment from previous assessments to review specification limits. The change shall not result from unexpected events arising during manufacture e.g. new unqualified impurity; change in total impurity limits.	Amendment of the relevant section(s) of the dossier for the new test method, validation and batch data, as appropriate. Comparative table of former and new in-process tests and limits.
a)	- tightening of in-process limits	The change shall be within the range of currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor.	
b)	addition of a new in-process test and limits	Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way. The new test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological active substance, except if this method is a standard pharmacopoeial microbiological method.	
11	Change in the specification parameters or limits of an active substance, starting material, intermediate or reagent used in the manufacturing process of the active substance or of the immediate packaging of the active substance	The change shall not result from unexpected events arising during manufacture (e.g. new unqualified impurity or change in total impurity limits). The change shall not be a consequence of any commitment from previous assessments to review specification	Amendment of the relevant section(s) of the dossier. Comparative table of former and new specification parameters and limits.

		limits (e.g. made during the procedure for the application for registration or a variation procedure not requiring assessment) unless it has been previously assessed and agreed as part of a follow-up measure in a previous procedure	
a)	- tightening of specification limits of an active substance, starting material, intermediate or reagent used in the manufacturing process of the active substance	The test procedure shall remain the same, or changes in the test procedure shall be minor. The change shall be within the range of currently approved limits.	
b)	- tightening of specification limits of the immediate packaging of the active substance	The test procedure shall remain the same, or changes in the test procedure shall be minor.	
c)	- addition of a new specification parameter to the specification with its corresponding test method	The new test method shall not concern a novel non-standard technique or a standard technique used in a novel way. The new test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological active substance, except if this method is a standard pharmacopoeial microbiological method. The change shall not concern a genotoxic impurity.	Amendment of the relevant section(s) of the dossier for the new method and validation, and batch data, as appropriate.
12	**Minor changes:**		
a)	to an approved test procedure - for active substance; - for the finished product; - for the immediate packaging of the active substance or the finished product;	The test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological active	Amendment of the relevant section(s) of the dossier and comparative validation data, as appropriate.

	- of a measuring or administration device	substance. Appropriate validation studies shall have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure. There shall be no changes of the total impurity limits; no new unqualified impurities shall be detected. The method of analysis shall remain the same (e.g. a change in column length or temperature, but not a different type of column or method).	
b)	- to an approved test procedure - for a starting material, reagent or intermediate used in the manufacturing process of the active substance; - for an excipient	The test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological active substance. Appropriate validation studies shall have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure. There shall be no changes of the total impurity limits; no new unqualified impurities shall be detected. The method of analysis shall remain the same (e.g. a change in column length or temperature, but not a different type of column or method).	Amendment of the relevant section(s) of the dossier and comparative data, as appropriate.

c)	- to an approved test procedure for an in-process test - for active substance; - for the finished product	The test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological active substance. Appropriate validation studies shall have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure. There shall be no changes of the total impurity limits; no new unqualified impurities shall be detected. The method of analysis shall remain the same (e.g. a change in column length or temperature, but not a different type of column or method).	Amendment of the relevant section(s) of the dossier.
d)	- in the manufacturing process of an active substance	The change shall not be applicable to a biological or immunological active substance. The change shall not be a change in the geographical source, manufacturing route or production for a herbal medicinal substance. The change shall relate only to an immediate release solid oral dosage form or oral solution and shall not provoke an adverse change in qualitative and quantitative impurity profile or in physico-chemical properties. The active substance and all intermediates, reagents, catalysts or solvents shall	Amendment of the relevant section(s) of the dossier.

		still conform to the approved specifications. The change shall not refer to the restricted part of an ASMF. The manufacturing steps shall remain the same.	
e)	- in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier) or a novel excipient	The excipients and all intermediates, reagents, catalysts, solvents or in-process controls shall still conform to the approved specifications (e.g. qualitative and quantitative impurity profile). Adjuvants and preservatives shall be excluded from the scope of this entry. Synthetic routes and specifications shall be identical, and there shall be no change in physico-chemical properties.	Amendment of the relevant section(s) of the dossier for batch data, comparative data, and specification, as appropriate.
f)	- to an in-process limit range for the finished product	The change shall not be the result of unexpected events arising during manufacture or because of stability concerns. The change shall concern an in-process test, which is also part of the finished product specification at release, and the new in-process limit range shall be within the approved release limit.	Amendment of the relevant section(s) of the dossier. Comparative table of former and new in-process limits.
g)	- to an approved change management protocol of the active substance that does not change the strategy defined in the protocol	The intermediates, reagents, catalysts or solvents used in the process shall remain the same. The active substance and all intermediates, reagents, catalysts or solvents shall still conform to the approved specifications. There shall be no adverse	Amendment of the relevant section(s) of the dossier.

		change in qualitative and quantitative impurity profile or in physico-chemical properties. The change shall not refer to the restricted part of an ASMF. The changes shall be within the range of currently approved limits. In case of biological products, this change shall be only possible if comparability is not required. Changes in the geographical source, manufacturing route or production of a herbal substance or herbal preparation of a herbal medicinal product shall be excluded.	
13	Changes to a test procedure (including replacement or addition) for a reagent used in the manufacturing process of the active substance or immediate packaging of the active substance:	The new test method shall not concern a novel non-standard technique or a standard technique used in a novel way.	Amendment of the relevant section(s) of the dossier for comparative validation data, as appropriate.
a)	- for a reagent, which does not have a significant effect on the overall quality of the active substance	The active substance shall not be a biological or immunological substance. There shall be no changes to the total impurity limits; no new unqualified impurities shall be detected. The method of analysis shall remain the same (e.g. a change in column length or temperature, but not a different type of column or method). Appropriate validation studies, performed in accordance with the relevant guidelines, shall show that the updated test procedure is at least	

		equivalent to the former test procedure.	
b)	- for the immediate packaging of the active substance	The active substance shall not be a biological or immunological substance. When the change concerns replacement of a method, the change shall not be a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the application for registration or a variation procedure not requiring assessment unless it has been previously assessed and agreed as part of a follow-up measure in a previous procedure	A document listing the comparative validation results or, if justified, the comparative analysis results, showing that the former test and the new one are equivalent.
14	Change in qualitative or quantitative composition of the immediate packaging for the active substance	Sterile or liquid formulations or biological or immunological active substances shall be excluded. The new packaging material shall be at least equivalent to the approved material in respect of its relevant properties and no interaction shall occur between the content and the packaging material. Stability studies shall have been started according to the current approved stability protocol and under International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) conditions; relevant	Amendment of the relevant section(s) of the dossier including stability confirmation. If the new packaging is more resistant than the former packaging, studies which have only started shall be finalised and the data shall be provided immediately afterwards to the competent authorities.

		stability parameters shall have been assessed in at least two pilot scale or industrial scale batches, and at least three months satisfactory stability data shall be at the disposal of the applicant. The stability profile shall be similar to the currently registered situation. However, if the new packaging is more resistant than the existing packaging, the three months' stability data do not yet have to be available.	
16	Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking of the finished product	The change shall not affect the delivery, use or safety of the finished product. The finished product release and shelf life specifications shall not have been changed except for appearance. The ink shall comply with the relevant pharmaceutical legislation. The change shall not relate to a scored tablet that is intended to be divided into equal doses.	Amendment of the relevant section(s) of the dossier.
17	Change in the shape or dimensions of the pharmaceutical form for immediate release tablets, capsules, suppositories and pessaries	The dissolution profile of the product shall remain unchanged. For herbal medicinal products, where dissolution testing may not be feasible the new disintegration time of the product shall be comparable to the former one. The release and end of shelf-life specifications of the product shall not have been changed. The qualitative or quantitative	Amendment of the relevant section(s) of the dossier.

		composition and mean mass shall remain unchanged. The change shall not relate to a scored tablet that is intended to be divided into equal doses.	
18	Change(s) in the composition (excipients) of a non-sterile finished product	The change shall not be applicable to a biological or immunological medicinal product. The change shall not have the potential to affect the identity, strength, quality, purity, potency, physical characteristics, safety or effectiveness of the finished product. Stability studies shall have been started according to the current approved stability protocol and under International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) conditions; relevant stability parameters shall have been assessed in at least two pilot scale or industrial scale batches, and at least three months satisfactory stability data shall be at the disposal of the applicant. The stability profile shall be similar to the currently registered situation.	Amendment of the relevant section(s) of the dossier including stability confirmation. Updated relevant pages of the MC8 form. Updated SmPC, labelling and package inserts
a)	- increase or reduction of a component or components of the flavouring or colouring system	Quantitative change(s) shall not exceed +/- 10 % of the existing concentration of the component. There shall be no change in functional characteristics of the pharmaceutical	

		form (e.g. disintegration time, dissolution profile). The finished product specification shall only have been updated in respect of appearance, odour or taste and, if relevant, deletion of an identification test. For veterinary medicinal products for oral use, the change shall not negatively affect the uptake by target animal species.	
b)	- any minor adjustment of the quantitative composition of the finished product with respect to excipients	Quantitative change(s) shall not exceed +/- 10 % of the existing concentration of the component. The change shall not affect the functional characteristics of the pharmaceutical form (e.g. disintegration time, dissolution profile). For solid oral dosage forms, the dissolution profile of the changed product shall be determined on a minimum of two pilot scale batches and shall be comparable to the former one. No significant differences regarding comparability shall occur. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the changed product shall be comparable to the former one. The change shall not be the result of stability issues and shall not result in potential safety concerns, e.g.	Amendment of the relevant section(s) of the dossier. 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 shall be included for each such material: name

		differentiation between strengths.	of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use.
c)	- addition or replacement of a component or components of the flavouring or colouring system	The change shall not affect the functional characteristics of the pharmaceutical form (e.g. disintegration time, dissolution profile). For solid oral dosage forms, the dissolution profile of the changed product shall be determined on a minimum of two pilot scale batches and shall be comparable to the former one. No significant differences regarding comparability shall occur. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the changed product shall be comparable to the former one. The change shall not be the result of stability issues and shall not result in potential safety concerns (e.g. differentiation between strengths).	Amendment of the relevant section(s) of the dossier. 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 shall 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.
19	Change in coating weight of oral dosage forms or change in weight of capsule shells for a solid oral pharmaceutical form	The change shall not be the result of stability issues and shall not result in potential safety concerns (e.g. differentiation between strengths). For veterinary medicinal products for oral use, the coating shall not be a critical factor for the release mechanism and the change shall not affect the uptake by target animal species. The finished product specification shall only be updated in respect of weight and dimensions, if applicable. The dissolution profile of the changed product shall be determined on a minimum of two pilot scale batches and shall be comparable to the former one. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the changed product shall be comparable to the former one. Relevant stability studies shall have been started under VICH conditions and relevant stability parameters shall have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data shall be at the disposal of the applicant at time of implementation.	Amendment of the relevant section(s) of the dossier including stability confirmation.

20	Replacement or addition of a primary packaging site of a non-sterile finished product	The change shall not be applicable to a biological or immunological medicinal product. The site shall be appropriately authorised to manufacture the pharmaceutical form or product concerned and satisfactorily inspected. The validation scheme shall be available or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches, as appropriate. If the manufacturing site and the primary packaging site are different, conditions of transport and bulk storage shall be specified and validated. The change only be applicable to manufacturing site from well-regulated VICH regions	Amendment of the relevant section(s) of the dossier.
21	Replacement or addition of a secondary packaging site of a finished product	The site shall be appropriately authorised to manufacture the pharmaceutical form or product concerned and satisfactorily inspected.	Amendment of the relevant section(s) of the dossier.
22	Change to importer, batch control arrangements and quality testing (replacement or addition of a site) for a finished product	The site shall be appropriately authorised and satisfactorily inspected. The change shall not be applicable to a biological or immunological medicinal product. Method transfer from the former to the new site shall have been successfully completed. The change only be	

		applicable to manufacturing site from well-regulated VICH regions	
23	Replacement or addition of a manufacturer of a finished product responsible for importation	The site shall be appropriately authorised and satisfactorily inspected. The change only be applicable to manufacturing site from well-regulated VICH regions	
24	Replacement or addition of a manufacturer responsible for batch release including batch control or testing of a non- sterile finished product	The site shall be appropriately authorised and satisfactorily inspected. The change shall not be applicable to a biological or immunological medicinal product. Method transfer from the former to the new site shall have been successfully completed. The change only be applicable to manufacturing site from well-regulated VICH regions	
25	Change in the packaging material of bulk product (intermediate product) not in contact with the bulk product formulation (including replacement or addition)	The manufacturing steps shall remain the same. The finished product, intermediates or in-process controls used in the manufacture of the finished product shall still conform to the approved specifications. The secondary packaging shall not play a functional role on the stability of the bulk product, or if it does, it shall not be less protective than the approved one.	Amendment of the relevant section(s) of the dossier
26	Change in the batch size (including batch size ranges) of the finished product:	The change shall not be applicable to a biological or immunological medicinal product. The	Amendment of the relevant section(s) of the dossier. Where relevant, the

		change shall not be the result of unexpected events arising during manufacture or because of stability concerns. The change shall not affect reproducibility or consistency of the product. The changes to the manufacturing method or to the in-process controls shall be only those necessitated by the change in batch-size, e.g. use of different sized equipment. A validation scheme shall be available or a validation of the manufacture shall have been successfully carried out according to the current protocol with at least three batches of the new batch size in accordance with the relevant guidelines.	batch numbers, corresponding batch size, the manufacturing date of batches (3) used in the validation study and the validation data or the validation protocol (scheme) shall be provided.
a)	- up to 10-fold increase compared to the originally approved batch size of an immediate release oral pharmaceutical forms or of a non-sterile liquid based pharmaceutical form	The batch size shall be within the 10-fold range of the batch size foreseen when the registration was granted.	
b)	- up to 10-fold increase compared to the originally approved batch size for the pharmaceutical form medicinal gas	The batch size shall be within the 10-fold range of the batch size foreseen when the registration was granted.	
c)	- downscaling down to 10-fold compared to the originally approved batch size of an immediate release oral pharmaceutical forms or to non-sterile liquid based pharmaceutical form	The batch size shall be within the 10-fold range of the batch size foreseen when the registration was granted.	
d)	- downscaling down to 10-fold (for the pharmaceutical form medicinal gas	The batch size shall be within the 10-fold range of the batch size foreseen	

		when the registration was granted.	
e)	- more than 10-fold increase compared to the originally approved batch size for an immediate release, solid oral pharmaceutical form		3 months stability data for at least one pilot batch under VICH condition.
27	Change to in-process tests or limits applied during the manufacture of the finished product:	The change shall not relate to a commitment or to an unexpected event during manufacture. The change shall not have the potential to affect the identity, strength, quality, purity, potency or physical characteristics of the finished product, intermediates or in-process materials.	Comparative table of former and new in-process tests or limits.
a)	- tightening of in-process limits	The change shall be within the range of currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor.	Amendment of the relevant section(s) of the dossier.
b)	- addition of a new in-process test and limits	Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way. The new test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological active substance, except if this method is a standard pharmacopoeial microbiological method.	Amendment of the relevant section(s) of the dossier for method and validation, batch data and relevant comparative data.
28	Change in the specification parameters or limits of an excipient	The change shall not be a consequence of any commitment from previous assessments to review specification limits. The change shall	

		not be a result of unexpected events arising during manufacture, e.g. new unqualified impurity or change in total impurity limits.	
a)	- tightening of specification limits	The change shall be within the range of currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor.	
b)	- addition of a new specification parameter to the specification with its corresponding test method	Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way. The new test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological active substance, except if this method is a standard pharmacopoeial microbiological method. The change shall not concern a genotoxic impurity.	Amendment of the relevant section(s) of the dossier for method and validation, batch data and relevant comparative data.
29	Change in source of an excipient or reagent with TSE risk from material with TSE risk to vegetable or synthetic origin	The excipient, finished product release and end of shelf life specifications shall remain the same. The change shall not concern an excipient or reagent used in the manufacture of a biological or immunological active substance or in a biological or immunological medicinal product.	Amendment of the relevant section(s) of the dossier. Declaration from the manufacturer or the applicant of the material that it is purely of vegetable or synthetic origin.

30	Change in the specification parameters or limits of the finished product:	The change shall not be a consequence of any commitment from previous assessments to review specification limits. The change shall not result from unexpected events arising during manufacture, e.g. new unqualified impurity or change in total impurity limits.	Amendment of the relevant section(s) of the dossier. Comparative table of former and new specification parameters and limits.
a)	- tightening of specification limits	The change shall be within the range of currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor.	
b)	- tightening of specification limits for finished products	The change shall be within the range of currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor.	
c)	- addition of a new specification parameter to the specification with its corresponding test method	Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way. The test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent for a biological active substance except if this method is a standard pharmacopoeial microbiological method. The change shall not concern any impurities (including genotoxic) or dissolution.	Amendment of the relevant section(s) of the dossier for method and validation, batch data and relevant comparative data.
d)	- update of the dossier to comply with the provisions of an updated	The change shall be within the range of	

	general monograph of the pharmacopoeia for the finished product, e.g., Ph.Eur, USP	currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor. The change shall not concern any impurities (including genotoxic) or dissolution.	
31	Uniformity of dosage units is introduced to replace the currently registered method	The change shall follow changes to the relevant pharmacopoeia monograph	Amendment of the relevant section(s) of the dossier. Comparative table of former and new specification parameters and limits.
32	Change in the specification parameters or limits of the finished product to describe more accurately the appearance of the product	The change shall not be a result of any unexpected events arising during manufacture or testing of the finished product.	Amendment of the relevant section(s) of the dossier. Comparative table of former and new specification parameters and limits. Updated relevant pages of the MC8 form. Updated SmPC, labelling and package inserts
33	Change in test procedure for the finished product to comply with a pharmacopoeia, e.g., Ph. Eur., USP:	The change shall not concern changes of the total impurity limits; no new unqualified impurities shall be detected. The method of analysis shall remain the same (e.g. a change in column length or temperature, but not a different type of column or method). The test method shall not be a biological, immunological or immunochemical method, or a method using a biological reagent	Amendment of the relevant section(s) of the dossier.

		for a biological active substance, except if this method is a standard pharmacopoeial microbiological method.	
a)	- update of the test procedure to comply with the updated general monograph in the pharmacopoeia, e.g., Ph. Eur., USP		
b)	- update of the test procedure to reflect compliance with the pharmacopoeia, e.g., Ph. Eur., USP and remove reference to the outdated internal test method and test method number		
34	Change in qualitative and quantitative composition of the immediate packaging for a solid pharmaceutical form for a finished product	For solid pharmaceutical forms, the change shall only concern the same packaging or container type (e.g. blister to blister). The finished product shall not be sterile. The change shall not affect the delivery, use, safety or stability of the finished product. Relevant stability studies shall have been started under VICH conditions and relevant stability parameters shall have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data shall be at the disposal of the applicant at time of implementation. However, if the new packaging is more resistant than the existing packaging, the three months' stability data do	Amendment of the relevant section(s) of the dossier. Comparative table of former and new immediate packaging specifications, permeability data and interaction data, as appropriate.

		not yet have to be available. The new packaging material shall be at least equivalent to the approved material in respect of its relevant properties.	
35	Change in the specification parameters or limits of the immediate packaging of the finished product:	The changes shall not be a consequence of any commitment from previous assessments to review specification limits. The change shall not result from unexpected events arising during manufacture.	Comparative table of former and new specifications or limits.
a)	- tightening of specification limits	The change shall be within the range of currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor.	
b)	- addition of a new specification parameter to the specification with its corresponding test method	Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way.	Amendment of the relevant section(s) of the dossier for method and validation and batch data, as appropriate.
36	Change in test procedure for the immediate packaging of the finished product (including replacement or addition)	The change shall not be applicable to a biological or immunological medicinal product. Appropriate validation studies shall have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure. Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way.	Amendment of the relevant section(s) of the dossier for method and validation and batch data, as appropriate.

37	Change in shape or dimensions of the container or closure (immediate packaging) of a non-sterile finished product	The change shall not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product. The change shall not concern the qualitative or quantitative composition of the container. In case of a change in the headspace or a change in the surface/volume ratio, stability studies in accordance with the relevant guidelines shall have been started, relevant stability parameters shall have been assessed in at least two pilot scale or industrial scale batches, and at least three months stability data shall be at the disposal of the applicant.	Amendment of the relevant section(s) of the dossier.
38	Change in pack size (number of units e.g. tablets, ampoules, etc. in a pack) within the range of the currently approved pack size	The new pack size shall be consistent with the posology and treatment duration as approved in the Summary of Product Characteristics. The primary packaging material shall remain the same.	
39	Change in any part of the primary packaging material not in contact with the finished product formulation (such as change of colour due to different plastic used for flip-off caps, colour code rings on ampoules or change of needle shield)	The change shall not concern a part of the packaging material that affects the delivery, use, safety or stability of the finished product.	Amendment of the relevant section(s) of the dossier.
40	Replacement or addition of a supplier of packaging components or devices (when mentioned in the dossier)	The qualitative and quantitative composition of the packaging components or device and	Amendment of the relevant section(s) of the dossier.

		design specifications shall remain the same. The change shall not have the potential to affect the identity, quality or purity of the packaging component or devices.	
41	Change in the shelf-life or to an approved stability protocol of the finished product:	The change shall not be the result of unexpected events arising during manufacture or because of stability concerns.	Amendment of the relevant section(s) of the dossier.
a)	- reduction of the shelf life of the finished product as packaged for sale, after first opening or after dilution or reconstitution		Updated labelling, package inserts and SmPC
b)	- change to an approved stability protocol	The change shall not have the potential to affect the identity, strength, quality, purity, potency or physical characteristics of the finished product. The change shall not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.	
42	Implementation in practice of changes already foreseen in an approved change management protocol (CMP) for the finished product	The change shall be in accordance with the approved CMP and the results of studies performed indicate that the predefined acceptance criteria specified in the protocol are meet. The implementation of the change shall require no further supportive data to the CMP.	
43	Editorial changes to part 2 of the dossier if inclusion in an upcoming procedure concerning part 2 is not possible		Comparative table of the changes to the dossier.

44	Submission of a new or updated Ph. Eur. CEP from an already approved manufacturer for a non-sterile: - active substance; - starting material, reagent or intermediate used in the manufacturing process of the active substance; - excipient	The finished product release and end of shelf life specifications shall remain the same. The change shall not have the potential to affect the identity, quality, purity, potency or physical characteristics of the active substance, starting material, reagent or intermediate used in the manufacturing process of the active substance, or of the excipient. No additional data shall be required. The manufacturing process of the active substance, starting material, reagent, intermediate or excipient shall not include the use of material from human or animal origin. For a herbal substance or a herbal preparation the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) shall remain the same.	Amendment of the relevant section(s) of the dossier, including a copy of the updated Ph. Eur. CEP and QP declaration, as appropriate.
45	Submission of a new Ph. Eur. CEP from a new manufacturer (replacement or addition) for a non-sterile: - active substance; - starting material, reagent or intermediate used in the manufacturing process of the active substance; - excipient	The finished product release and end of shelf life specifications shall remain the same. The change shall not have the potential to affect the identity, quality, purity, potency or physical characteristics of the active substance, starting material, reagent or intermediate used in the manufacturing process of the active substance, or of the excipient. No additional data shall be required. The	Amendment of the relevant section(s) of the dossier, including a copy of the updated Ph. Eur. CEP and QP declaration, as appropriate.

		manufacturing process of the active substance, starting material, reagent, intermediate or excipient shall not include the use of material from human or animal origin. For a herbal substance or a herbal preparation the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) shall remain the same.	
46	Submission of a new or updated Ph. Eur. TSE CEP for a non-sterile: - active substance; - starting material, reagent, intermediate used in the manufacturing process of the active substance; - excipient	The change shall not have the potential to affect the identity, quality, purity, potency or physical characteristics of the active substance, starting material, reagent or intermediate used in the manufacturing process of the active substance, or of the excipient. The change shall not impact the risk of extraneous agents contamination (e. g. no change of country of origin).	Amendment of the relevant section(s) of the dossier including a copy of the updated Ph. Eur. CEP, QP declaration and TSE information, as appropriate.
47	Change to comply with a pharmacopoeia:	The change shall be made exclusively to fully comply with the pharmacopoeia. All the tests in the specification shall correspond to the pharmacopoeial standard after the change, except any additional tests. Additional validation of a new or changed pharmacopoeial method shall not be required. For a herbal substance or a herbal preparation the manufacturing route, physical form, extraction solvent and drug extract	Amendment of the relevant section(s) of the dossier. Comparative table of the former and new specifications, if applicable.

		ratio (DER) shall remain the same.	
a)	- change of specification(s) of a former non Pharmacopoeial active substance, excipient or active substance starting material to fully comply with the pharmacopoeia	Additional specifications to the pharmacopoeia for product specific properties shall be unchanged (e.g. particle size profiles, polymorphic form, bioassays or aggregates). The change shall not concern significant changes in qualitative and quantitative impurities profile unless the specifications are tightened.	Batch data and data demonstrating the suitability of the monograph to control the substance.
b)	- change to comply with an update of the relevant monograph of the pharmacopoeia	Additional specifications to the pharmacopoeia for product specific properties shall be unchanged (e.g. particle size profiles, polymorphic form, bioassays or aggregates).	
c)	- to reflect compliance with the pharmacopoeia by removing reference to the internal test method and test method number		
48	Addition or replacement of a measuring or administration device which is not an integrated part of the primary packaging	The change shall not affect the delivery, use, safety or stability of the finished product. The change shall be only applicable to a device with CE marking. The new measuring or administration device shall accurately deliver the required dose for the product concerned in line with the approved posology, and results of such studies shall be available. The new device shall be compatible with the veterinary medicinal	Amendment of the relevant section(s) of the dossier.

		product. The change shall not lead to substantial amendments of the product information.	
49	Change in specification parameters or limits of a measuring or administration device:	The change shall not be a consequence of any commitment from previous assessments to review specification limits. The change shall not be the result of unexpected events arising during manufacture.	Amendment of the relevant section(s) of the dossier. Comparative table of former and new specification parameters and limits.
a)	- tightening of specification limits	The change shall be within the range of currently approved limits. The test procedure shall remain the same, or changes in the test procedure shall be minor.	
b)	- addition of a new specification parameter to the specification with its corresponding test method	Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way.	Amendment of the relevant section(s) of the dossier for method and validation and batch data.
50	Change in test procedure (including replacement or addition) of a measuring or administration device	Appropriate validation studies shall have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure. Any new test method shall not concern a novel non-standard technique or a standard technique used in a novel way.	Amendment of the relevant section(s) of the dossier for method and validation and batch data.
51	Update of the quality dossier	This change shall only be applicable when no new or additional data is required for an assessment.	Amendment of the relevant section(s) of the dossier.
C	Changes to the safety, efficacy and pharmacovigilance part of the dossier		

1	Change(s) in the name or address or contact details of a qualified person for pharmacovigilance (QPPV)		
2	Change(s) in the Summary of Product Characteristics (SPC), labelling or package leaflet	This change shall only be applicable when no new or additional data is required for an assessment.	
3	Change(s) in the SPC, labelling or package leaflet of a generic or hybrid medicinal product following assessment of the same change(s) for the reference product	This change shall only be applicable when no new or additional data is required for an assessment. The proposed changes to Summary of Product Characteristics, Labelling and Package Leaflet shall be identical to those changes approved for the reference medicinal product.	
4	Change in the pharmacovigilance system master file (PSMF) location		
5	Introduction of a summary of the PSMF or changes to the summary of the PSMF		Summary of pharmacovigilance system master file
6	Introduction of, or change(s) to, the obligations and conditions of registration, including the risk management plan	The wording shall be limited to that agreed by the Authority	
7	Implementation of changes in the SPC not already covered elsewhere	This change shall only be applicable when no new or additional data is required for an assessment. The changes shall not affect the quality, safety or efficacy of the product. Changes shall be minor in nature and shall be consistent with the information currently included in the SPC.	
8	Editorial changes to SPC, package leaflet or labelling if	The changes shall not affect the quality, safety	

	inclusion in an upcoming procedure is not possible	or efficacy of the medicinal product.	
9	Changes to the labelling or the package leaflet which shall not be connected with the SPC:		
a)	- administrative information concerning the holder's representative	Changes shall be minor in nature and shall be consistent with the information included in the SPC. The change shall not include the introduction of new batch release sites. Changes shall not be promotional in nature and shall not have a negative impact on the legibility of the product information.	
b)	- other changes	Changes shall be minor in nature and shall be consistent with the information included in the SPC. The change shall not include the introduction of new batch release sites. Changes shall not be promotional in nature and shall not have a negative impact on the legibility of the product information.	
c)	- inclusion of traceability stickers in or on product carton	Addition shall not have a negative impact on the legibility of the product information.	
D	Changes to the vaccine antigen master file (VAMF) part of the dossier		
1	Change in the name or address or contact details of the VAMF certificate holder for biological products	The applicant shall remain the same legal entity.	Amendment of the relevant section(s) of the dossier, as appropriate.
2	Inclusion of an already certified VAMF in the approved dossier of a veterinary medicinal product.	Changes shall not affect the properties of the finished product.	Amendment of the relevant section(s) of the dossier.

5.4 Variations Requiring Assessment

5.4.1 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**	**Time table**
	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').		

5.4.2 QUALITY CHANGES

5.4.2.1 ACTIVE SUBSTANCE

5.4.2.1 a) Manufacture

5.4.2.1.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		**S**

	bioavailability.		
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 pharmacopoeia 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**
Documentation			
1.	A declaration from the applicant 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 aslisted in the application form for registration.		

4.	Proof that the proposed site is appropriately authorised for the pharmaceutical form or product ormanufacturing operation concerned.

5.4.2.1.a.2 Changes in the manufacturing process of the activesubstance		**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**

Documentation	
1.	Amendment of the approved Active Substance Master File, including a direct comparison of thepresent 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 5.4.2.1.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.

5.4.2.1.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**
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 applicant if outside specification (with proposed action).		
3. Copy of approved specifications of the active substance (and of the intermediate, if applicable).		

5.4.2.1.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**
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 otherwisejustified) of the active substance for all specification parameters.		
4. Justification from the applicant or ASMF Holder as appropriate for the new in-process test and limits.		

5.4.2.1.b) Control of active substance

5.4.2.1.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 asa result of a safety or quality issue**	**1, 2, 3, 4, 5**	**R**
e)	**Where there is no monograph in Pharmacopoeia e.g. European Pharmacopoeia, USP**	**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**

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 otherwisejustified) 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 applicant or ASMF Holder as appropriate of the new specification parameter and thelimits.

(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 5.4.2.1.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 drugsubstance is considered to be a GMP issue and therefore information on whether the finished productmanufacturer 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.

5.4.2.1.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**
Documentation		
1. Description of the analytical methodology, a summary of validation data, revised specifications forimpurities (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 ofa new test procedure.		

5.4.2.1.c) Container closure system

5.4.2.1.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**
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		
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 contentand no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeia requirements		
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 3months, 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 specificationsat the end of the approved retest period (with proposed action).		

5.4.2.1.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**
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 applicant or the ASMF Holder, as appropriate, of the newspecification parameter and the limits.		

5.4.2.1.d) Stability

5.4.2.1.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 ofthe active substance in the authorised packaging material and covering the duration of the requestedre-test period or requested storage conditions.		
2. Confirmation that stability studies have been done to the currently approved protocol. The studiesmust 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		

5.4.2.1.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 ofthe 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 studiesmust show that the agreed relevant specifications are still met.		
3. Copy of approved specifications of the active substance.		

5.4.2.1.e) Design Space and post-approval change management protocols

5.4.2.1.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 VICH 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 systematicmechanistic 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.		

5.4.2.1.e.2 Changes to a post approval change management pro **related to the active substance**	**Documentation to besupplied**	**Timetable**
a) Introduction of a post approval change management protocol related to the active	**1, 2**	**S**

substance		
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 requiresfurther 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 studyresults 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.		

5.4.2.1.f) Other changes to the active substance

5.4.2.1.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 5.4.2.1.f.1		

5.4.2.2 FINISHED PRODUCT

5.4.2.2.a) Description and composition

5.4.2.2.a.1 Change or addition of imprints, bossing or other markings including replacement, or addition of inks usedfor product marking.	**Documentation to be supplied**	**Timetable**
a) Changes in scoring/break lines intended to divide into equal doses	**1, 2, 3**	**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 pharmacopoeia tests demonstrating equivalence in characteristics/correct dosing.

5.4.2.2.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**
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 (nosignificant differences regarding comparability see the relevant guidance on bioavailability/bioequivalence). For herbal medicinal product comparative disintegration data may beacceptable.		
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 pharmacopoeia tests demonstrating equivalence in characteristics/correct dosing.		

5.4.2.2.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 the colouring or flavouring agent is important for the uptake by target animal		**S**

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**

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 beincluded for each such material: Name of manufacturer, species and tissues from which the materialis a derivative, country of origin of the source animals and its use.
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 thefinished 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 accordingto 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.

5.4.2.2.a.4 Change in coating weight of oral dosage forms orchange 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**

5.4.2.2.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

5.4.2.2.b) Manufacture

5.4.2.2.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 veterianary 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**

Documentation
1. Proof that the proposed site is appropriately authorised for the pharmaceutical form or product concerned.
2. Where relevant, the batch numbers, corresponding batch size and the manufacturing date of batches (3) used in the validation study should be indicated and the validation data presented, or validation protocol (scheme) to be submitted.
3. The variation application documentation should clearly outline the "present" and "proposed" finished product manufacturers .
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 productionprocess (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 startingmaterials ii) In addition, if the new manufacturing site 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.
8. If the manufacturing site and the primary packaging site are different, conditions of transport andbulk storage should be specified and validated.

5.4.2.2.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**
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**

5.4.2.2.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 terminalsterilisation 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**

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 visiblechanges 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 onbioavailability/bioequivalence.
5. For changes to process parameter(s) that have been considered to have no impact on the quality ofthe finished product, declaration to this effect reached in the context of the previously approved riskassessment.
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 productionbatches should be made available upon request and reported by the applicant 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 finalized 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).

5.4.2.2.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**

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 applicant 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 providedimmediately 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.

5.4.2.2.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**
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.		

5.4.2.2.c) Control of excipients

5.4.2.2.c.1 Change in the specification parameters and/orlimits 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, asa result of a safety or quality issue	**1, 2, 3, 4, 5, 6**	**R**
d) Where there is no monograph in the Pharmacopoeia e.g., European, USP	**1, 2, 3, 4, 5, 6**	**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 pilotbatch 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.

5.4.2.2.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**
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.		

5.4.2.2.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**
Documentation		
1. Declaration from the manufacturer or the applicant of the material that it ispurely of vegetable or synthetic origin.		
2. Study of equivalence of the materials and the impact on production of the final material and impacton behaviour (e.g. Dissolution characteristics) of the finished product.		

5.4.2.2.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**

5.4.2.2.d) Control of finished product

5.4.2.2.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**
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 pilotbatch 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		

5.4.2.2.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**
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.

5.4.2.2.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

5.4.2.2.e) Container closure system

5.4.2.2.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**

Documentation
1. Appropriate data on the new packaging (comparative data on permeability e.g. for O_2, CO_2moisture).
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.
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 Authority 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.

5.4.2.2.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**
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.		

5.4.2.2.e.3 Change in shape or dimensions of the container orclosure (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**
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 batchnumbers 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 therequired 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 atthe 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 Authority if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).		

5.4.2.2.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**
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), applicants are reminded that any change to the 'strength' of the medicinal product is classified as a variation under chapter I of this annex.		

5.4.2.2.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**

5.4.2.2.e.7 Change in supplier of packaging components ordevices (when mentioned in the dossier)	**Documentation to be supplied**	**Timetable**
a) Any change to suppliers of spacer devices for metered dose inhalers		**S**

5.4.2.2.f) Stability

5.4.2.2.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 ion accordance with an approved stability protocol.	**1, 2**	**R**
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**
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 finishedproduct in the authorized packaging material and/or after first opening or reconstitution, as appropriate; where applicable, results of appropriate microbiological testing should be included. [1]Pilot scale batches can be accepted with a commitment to verify the shelf life on production scalebatches.		
2. Copy of approved end of shelf life finished product specification and where applicable, specificationsafter dilution/reconstitution or first opening.		
*Note: extrapolation not applicable for biological/immunological medicinal product		

5.4.2.2.g) Design Space and post approval change management protocol

5.4.2.2.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 multivariatestudies, as appropriate) demonstrating that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the finished product has beenachieved.		
2. Description of the design space in tabular format, including the variables (material attributes andprocess parameters, as appropriate) and their proposed ranges.		

5.4.2.2.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 changemanagement 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 requiresfurther 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.

5.4.2.3 CEP/TSE/MONOGRAPHS

5.4.2.3.1 Submission of a new or updated Ph. Eur. certificateof suitability or deletion of Ph. Eur. certificate of suitability: **For an active substance** **For a starting material/reagent/intermediate usedin the manufacturing process of the active substance** **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**
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 materialsof human or animal origin for which an assessment of the risk with respect to potential contamination with adventitious agents is required		**S**
Documentation		
1. Copy of the current (updated) Ph. Eur. Certificate of Suitability.		
2. In case of an addition of a manufacturing site, the variation documentation should clearly outline the "present" and "proposed" manufacturers.		
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.		
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 astarting 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.		
5. Suitable evidence to confirm compliance of the water used in the final steps of the synthesis of theactive substance with the corresponding requirements on quality of water for pharmaceutical use.		

5.4.2.4 DEVICES

5.4.2.4.1 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**
Documentation		
1. Description, detailed drawing and composition of the device material and supplier whereappropriate.		
2. Data to demonstrate accuracy, precision and compatibility of the device.		
3. Samples of the new device where applicable.		

5.4.2.4.2 Change in specification parameters and/or limits ofa 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		

5.4.2.5 CHANGES TO CONDITIONS OF REGISTRATION /APPROVAL RESULTING FROM OTHER REGULATORY PROCEDURES

5.4.2.5.a) VAMF/PTMF

5.4.2.5.a.1 Inclusion of a new, updated or amended Vaccine Antigen Master File in the authorizedonapproved dossierof 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 authorized product, VAMF holder has submitted the VAMF Certificate, Evaluation report and VAMF dossier to the applicant (where the applicant is different to the VAMF holder), the VAMF Certificate and Evaluation Report replace the previous VAMF documentation for this registration.		
2. VAMF Certificate and Evaluation Report.		
3. An expert statement outlining all the changes introduced with the certified VAMF and evaluatingtheir potential impact on the finished products including product specific risk assessments.		
4. The variation documentation should clearly outline the "present" and "proposed" VAMF EMA Certificate (code number) in the MA dossier. When applicable, the variation documentation should daylist also all the other VAMFs to which the medicinal product refers even if they are not the subject of the application.		

5.4.2.5.a.2 Inclusion of a new, updated or amended Platform Technology Master File in the approved 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**

5.4.2.5.b) Harmonisation of the quality dossier

5.4.2.5.b.1 Harmonisation of the quality dossier	**Documentation to be supplied**	**Timetable**
a) Harmonisation of the quality dossier after a European 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		**S**

5.4.3 SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES

5.4.3.1.1 Change(s) in the Summary of Product Characteristics, Labelling or Package	Documentation to be supplied	Timetable
a) The medicinal product is not covered by the defined scope of the Authority Decision but the change(s) implements the outcome of the Authority's Decision and nonew additional data is required to be submitted by the applicant	1, 2	R
b) The medicinal product is not covered by the defined scope of the Authority's Decision but the change(s) implements the outcome of the Authority's Decision with new additional data submitted by the applicant	1	S
Documentation		
1. Attached to the cover letter of the variation application: a reference to the Authority's 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 Leafletis identical for the concerned sections to that annexed to the Authority's Decision.		

5.4.3.2 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 applicant (e.g. comparability)		S
b) Harmonisation of the generic/hybrid product according to article 71(1) of the European Commission after SPC harmonisation of the reference product		S
c)		

5.4.3.3 Change(s) in the SPC, labelling or package leafletintended 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 applicant	**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/assessmentof the competent authority.		

5.4.3.4 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

5.4.3.5 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 VICH 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 thewording for one of the active substances was approved.		

5.4.3.7 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**

5.4.3.8 Introduction of, or change(s) to, the obligations and conditions of registration, including the riskmanagement 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 applicant 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 registration, including the risk management plan and the conditions and/or obligations of registration under exceptional circumstances.

5.4.3.9 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 ofthe 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.		

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

5.4.3.11 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		

5.4.3.12 Changes to the withdrawal period for a veterinary medicinal product	**Documentation to be supplied**	**Timetable**

		S

5.2.4.3 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**

6.0 KEY RELEVANT DOCUMENTS

6.1 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

6.2 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

7.0 HISTORY

DOCUMENT HISTORY		
Revision Number	Date Approved	New Document
N/A	N/A	

APPENDICES

APPENDIX I: Variations Not Requiring Assessment

5.3 VARIATIONS NOT REQUIRING ASSESSMENT		
Number	***Variation***	***Page Number***
A	**Administrative changes**	
1	Change in the name or address or contact details	
2	Change in the (invented) name of the veterinary medicinal product	
3	Change in name of the active substance or of an excipient	
B	**Changes to the quality part of the dossier**	
1	Change in the name or address or contact details of a supplier of a packaging component or of a device of the finished product	
2	Change in the nomenclature of the material for immediate packaging of the finished product	
3	Deletion of:	
a)	- a manufacturing site for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material for an active substance, reagent or excipient	
b)	- a manufacturing process for the active substance or the finished product, including an intermediate used in the manufacture of the finished product when an alternative is already approved	
c)	- a non-significant in-process test during the manufacture of the active substance	
d)	- a non-significant specification parameter of - an active substance; - a starting material; - an intermediate or reagent used in the manufacturing process of the active substance	
e)	- a test procedure - for the active substance or a starting material, reagent or intermediate of the active substance; - for the immediate packaging of the active substance; - for an excipient or the finished product; - for the immediate packaging of the finished product	

v)	- one of the authorised bulk or final containers or immediate packaging of the finished product that does not lead to the complete deletion of a strength or pharmaceutical form	-
w)	- a non-significant specification parameter in the specification parameters or limits of the immediate packaging of the active substance or the finished product	
x)	- an approved change management protocol related to the active substance or the finished product	
y)	- a component or components of the flavouring or colouring system	
z)	- a solvent or diluent container from the pack	
aa)	- a non-significant in-process test during the manufacture of the finished product	
bb)	details on testing frequency by the finished product manufacturer of an excipient or an active substance or of packaging material for the immediate packaging of an active substance or the finished product, when mentioned in the dossier	
cc)	- a non-significant specification parameter in the specification parameters or limits of an excipient	
dd)	a non-significant specification parameter in the specification parameters or limits of the finished product	
ee)	- a measuring or administration device	
ff)	- a non-significant specification parameter of a measuring or administration device	
gg)	- a test procedure of a measuring or administration device	
hh)	- pack size(s) of the finished product	
ii)	- a supplier of packaging components or devices	
jj)	- a Ph. Eur. CEP - for an active substance; - for a starting material, reagent or intermediate used in the manufacturing process of the active substance; - for an excipient	
kk)	- a Ph. Eur. Transmissible Spongiform Encephalopathy (TSE) CEP - for an active substance; - for a starting material, reagent or intermediate of an active substance; - for an excipient	

4	Changes to the production process or the storage of active substance where no Ph. Eur. CEP is part of the approved dossier of an active substance (including starting material, reagent or intermediate)	
5	Reduction of re-test period or storage period where no Ph. Eur. CEP covering the retest period is part of the approved dossier	
6	Change to more restrictive storage conditions:	
7	Change to an approved stability protocol of an active substance	
8	Implementation of changes foreseen in an approved change management protocol (CMP) for the active substance	
9	Change in batch size of active substance or intermediate used in the manufacturing process of the active substance	
10	Change to in-process tests or limits applied during the manufacture of the active substance	
11	Change in the specification parameters or limits of an active substance, starting material, intermediate or reagent used in the manufacturing process of the active substance or of the immediate packaging of the active substance	
12	**Minor changes:**	
h)	to an approved test procedure - for active substance; - for the finished product; - for the immediate packaging of the active substance or the finished product; - of a measuring or administration device	
i)	- to an approved test procedure - for a starting material, reagent or intermediate used in the manufacturing process of the active substance; - for an excipient	
j)	- to an approved test procedure for an in-process test - for active substance; - for the finished product	
k)	- in the manufacturing process of an active substance	
l)	- in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier) or a novel excipient	
m)	- to an in-process limit range for the finished product	
n)	- to an approved change management protocol of the active substance that does not change the strategy defined in the protocol	

13	Changes to a test procedure (including replacement or addition) for a reagent used in the manufacturing process of the active substance or immediate packaging of the active substance:	
14	Change in qualitative or quantitative composition of the immediate packaging for the active substance	
15	Addition of or change to a calendar package for a pack size already registered in the dossier	
16	Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking of the finished product	
17	Change in the shape or dimensions of the pharmaceutical form for immediate release tablets, capsules, suppositories and pessaries	
18	Change(s) in the composition (excipients) of a non-sterile finished product	
19	Change in coating weight of oral dosage forms or change in weight of capsule shells for a solid oral pharmaceutical form	
20	Replacement or addition of a primary packaging site of a non-sterile finished product	
21	Replacement or addition of a secondary packaging site of a finished product	
22	Change to importer, batch control arrangements and quality testing for a finished product	
23	Replacement or addition of a manufacturer of a finished product responsible for importation	
24	Replacement or addition of a manufacturer responsible for batch release including batch control or testing of a non- sterile finished product	
25	Change in the packaging material of bulk product not in contact with the bulk product formulation	
26	Change in the batch size of the finished product:	
27	Change to in-process tests or limits applied during the manufacture of the finished product:	
28	Change in the specification parameters or limits of an excipient	
29	Change in source of an excipient or reagent with TSE risk from material with TSE risk to vegetable or synthetic origin	
30	Change in the specification parameters or limits of the finished product:	
31	Uniformity of dosage units is introduced to replace the currently registered method	

32	Change in the specification parameters or limits of the finished product to describe more accurately the appearance of the product	
33	Change in test procedure for the finished product to comply with Ph. Eur.:	
34	Change in qualitative and quantitative composition of the immediate packaging for a solid pharmaceutical form for a finished product	
35	Change in the specification parameters or limits of the immediate packaging of the finished product:	
36	Change in test procedure for the immediate packaging of the finished product	
37	Change in shape or dimensions of the container or closure of a non-sterile finished product	
38	Change in pack size within the range of the currently approved pack size	
39	Change in any part of the primary packaging material not in contact with the finished product formulation	
40	Replacement or addition of a supplier of packaging components or devices	
41	Change in the shelf-life or to an approved stability protocol of the finished product:	
42	Implementation in practice of changes already foreseen in an approved change management protocol (CMP) for the finished product	
43	Editorial changes to part 2 of the dossier if inclusion in an upcoming procedure concerning part 2 is not possible	
44	Submission of a new or updated Ph. Eur. CEP from an already approved manufacturer for a non-sterile: - active substance; - starting material, reagent or intermediate used in the manufacturing process of the active substance; - excipient	
45	Submission of a new Ph. Eur. CEP from a new manufacturer for a non-sterile: - active substance; - starting material, reagent or intermediate used in the manufacturing process of the active substance; - excipient	
46	Submission of a new or updated Ph. Eur. TSE CEP for a non- sterile: - active substance; - starting material, reagent, intermediate used in the manufacturing process of the active substance; - excipient	

47	Change to comply with a pharmacopoeia:	
48	Addition or replacement of a measuring or administration device which is not an integrated part of the primary packaging	
49	Change in specification parameters or limits of a measuring or administration device:	
50	Change in test procedure of a measuring or administration device	
51	Update of the quality dossier	
C	Changes to the safety, efficacy and pharmacovigilance part of the dossier	
1	Change(s) in the name or address or contact details of a qualified person for pharmacovigilance (QPPV)	
2	Change(s) in the Summary of Product Characteristics (SPC), labelling or package leaflet	
3	Change(s) in the SPC, labelling or package leaflet of a generic or hybrid medicinal product following assessment of the same change(s) for the reference product	
4	Change in the pharmacovigilance system master file (PSMF) location	
5	Introduction of a summary of the PSMF or changes to the summary of the PSMF	
6	Introduction of, or change(s) to, the obligations and conditions of registration, including the risk management plan	
7	Implementation of changes in the SPC not already covered elsewhere	
8	Editorial changes to SPC, package leaflet or labelling if inclusion in an upcoming procedure is not possible	
9	Changes to the labelling or the package leaflet which shall not be connected with the SPC:	
a)	- administrative information concerning the holder's representative	
b)	- other changes	
c)	- inclusion of traceability stickers in or on product carton	
D	Changes to the vaccine antigen master file (VAMF) part of the dossier	
1	Change in the name or address or contact details of the VAMF certificate holder for biological products	
2	Inclusion of an already certified VAMF in the registrationdossier of a veterinary medicinal product.	