	replacement of a biological reference preparation not covered by an approved protocol			
d)	**Other changes to a test procedure (including replacement or addition)**		**1, 2**	**IB**
e)	Update of the test procedure to comply with the updated general monograph in the Ph. Eur.	2, 3, 4, 5	1	IA
f)	To reflect compliance with the Ph.Eur. and remove reference to the internal test method and test method number	2, 3, 4, 5	1	IA

Conditions

1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.
2. There have been no changes of the total impurity limits; no new unqualified impurities are detected
3. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
4. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).
5. The registered test procedure already refers to the general monograph of the Ph. Eur and any changes are minor in nature and require updating of the dossier information.

Documentation

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

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

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Documentation ... [9]

B.II.e) Container closure system

B.II.e.1 Change in immediate packaging of the finished	**Conditions to**	**Documentation**	**Procedure**

product	be fulfilled	to be supplied	type
a) Qualitative and quantitative composition			
1. Solid pharmaceutical forms	**1, 2, 3**	**1, 2, 3, 4, 6**	**IA**
2. Semi-solid and non-sterile liqui pharmaceutical forms		**1, 2, 3, 5, 6**	**IB**
3. Sterile medicinal products and biological/ immunological medicinal products			**II**
4. The change relates to a less protective pack where there are associated changes in storage conditions and/or reduction in shelf life			**II**
b) Change in type of container or addition of a new container			
1. Solid, semi-solid and non-sterile liquid pharmaceutical forms		**1, 2, 3, 5, 6, 7**	**IB**
2. Sterile medicinal products and biological/ immunological medicinal products			**II**
3. Deletion of an immediate packaging container that does not lead to the complete deletion of a strength or pharmaceutical form	**4**	**1, 8**	**IA**
Conditions			
1. The change only concerns the same packaging/container type (e.g. blister to blister).			
2. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.			
3. Relevant stability studies have been started under ICH/VICH conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging e.g. thicker blister packaging, the three months' stability data do not yet have to be available. These studies must be finalised and the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).			
4. The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product			

information as appropriate.
2. Appropriate data on the new packaging (comparative data on permeability e.g. for O_2, CO_2 moisture).
3. Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeial requirements or legislation of the Union on plastic material and objects in contact with foodstuffs.
4. A declaration that the required stability studies have been started under ICH/VICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).
5. The results of stability studies that have been carried out under ICH/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).
6. Comparative table of the current and proposed immediate packaging specifications, if applicable.
7. Samples of the new container/closure where applicable (see NTA, Requirements for samples in the Member States/EMA).
8. Declaration that the new/remaining pack-size(s), is/are consistent with the dosage regimen and duration of treatment and adequate for the dosing instructions as approved in the summary of product characteristics
Note: For B.II.e.1.b) applicants are reminded that any change which results in a "new pharmaceutical form" requires the submission of an Extension application.

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Note: For B.II.e.1.b) applicants are reminded that any change which results in a "new pharmaceutical form" requires the submission of an Extension application. ... [10]

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

d) Addition or replacement of a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4, 6**	**IB**
Conditions			
1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure) unless the supporting documentation has been already assessed and approved within another procedure.			
2. The change does not result from unexpected events arising during manufacture			
3. Any change should be within the range of currently approved limits.			
4. The test procedure remains the same, or changes in the test procedure are minor.			
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).			
2. Comparative table of current and proposed specifications.			
3. Details of any new analytical method and validation data, where relevant.			
4. Batch analysis data on two batches of the immediate packaging for all specification parameters.			
5. Either a declaration from the marketing authorisation holder that the parameter is non-significant based on a previously approved risk assessment, or a justification that it is obsolete.			
6. Justification of the new specification parameter and the limits.			

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B.II.e.3 Change in test procedure for the immediate packaging of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor changes to an approved test procedure	**1, 2, 3**	**1, 2**	**IA**
b) Other changes to a test procedure (including replacement or addition)	**1, 3, 4**	**1, 2**	**IA**
c) Deletion of a test procedure if an alternative test procedure is already authorised	**5**	**1**	**IA**
Conditions			
1. Appropriate validation studies have been performed in accordance with the relevant guidelines and validation studies show that the updated test procedure is at least equivalent to the former test procedure.			

2.	The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method).
3.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
4.	The active substance/ finished product is not biological/immunological.
5.	An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA(IN) notification.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a description of the analytical methodology, a summary of validation data.
2.	Comparative validation results or if justified comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Non-sterile medicinal products	**1, 2, 3**	**1, 2, 4**	**IA**
b) The change in shape or dimensions concerns a fundamental part of the packaging material, which may have a significant impact on the delivery, use, safety or stability of the finished product			**II**
c) Sterile medicinal products		**1, 2, 3, 4**	**IB**
Conditions			
1. No change in the qualitative or quantitative composition of the container.			
2. The change does not concern a fundamental part of the packaging material, which affects the delivery**,** use, safety or stability of the finished product.			
3. In case of a change in the headspace or a change in the surface/volume ratio, stability studies in accordance with the relevant guidelines have been started and relevant stability parameters have been assessed in at least two pilot scale (three for biological/immunological medicinal products) or industrial scale batches and at least three months (six months for biological/immunological medicinal products) stability data are at the disposal of the applicant. Assurance is given that these studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).			

Documentation	
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including description, detailed drawing and composition of the container or closure material, and including revised product information as appropriate.	
2. Samples of the new container/closure where applicable (see NTA, Requirements for samples in the Member States).	
3. Re-validation studies have been performed in case of sterile products terminally sterilised. The batch numbers of the batches used in the re-validation studies should be indicated, where applicable.	
4. In case of a change in the headspace or a change in the surface/volume ratio, a declaration that the required stability studies have been started under ICH/VICH conditions (with indication of the batch numbers concerned) and that, as relevant, the required minimum satisfactory stability data were at the disposal of the applicant at time of implementation for a Type IA notification and time of submission of a Type IB notification, and that the available data did not indicate a problem. Assurance should also be given that the studies will be finalised and that data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the approved shelf life (with proposed action).	

B.II.e.5 Change in pack size of the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Change in the number of units (e.g. tablets, ampoules, etc.) in a pack			
1. Change within the range of the currently approved pack sizes	**1, 2,**	**1, 3, 4**	**IA_{IN}**
2. Change outside the range of the currently approved pack sizes		**1, 2, 3, 4**	**IB**
b) Deletion of pack size(s)	**3**	**1, 2**	**IA**
c) Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including biological/ immunological medicinal products			**II**
d) Change in the fill weight/fill volume of non-parenteral multi-dose (or single-dose, partial use) products		**1, 2, 3**	**IB**

Conditions
1. New pack size should be consistent with the posology and treatment duration as approved in the summary of product characteristics.

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2.	The primary packaging material remains the same.
3.	The remaining product presentation(s) must be adequate for the dosing instructions and treatment duration as mentioned in the summary of product characteristics.
Documentation	
1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate) including revised product information as appropriate.
2.	Justification for the new/remaining pack-size, showing that the new/remaining size is/are consistent with the dosage regimen and duration of treatment as approved in the summary of product characteristics.
3.	Declaration that stability studies will be conducted in accordance with the relevant guidelines for products where stability parameters could be affected. Data to be reported only if outside specifications (with proposed action).
4.	In case of multipack/ bundle pack, the multipack/ bundle pack must ensure that the packs remain together during transportation and in pharmacy and should contain all legally required labelling items for the outer packaging, including blue-box (BB) information. In addition, it should comply with the applicable guidance at EMA/CMD level.
Note: For B.II.e.5.c) and d), applicants are reminded that any changes to the 'strength' of the medicinal product require the submission of an Extension application.	

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B.II.e.6 Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used))	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Change that affects the product information	**1**	**1**	**IA_{IN}**
b) Change that does not affect the product information	**1**	**1**	**IA**
Conditions			
1. The change does not concern a part of the packaging material, which affects the delivery, use, safety or stability of the finished product.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including revised product information as appropriate.			

B.II.e.7 Change in supplier of packaging components or devices (when mentioned in the dossier)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Deletion of a supplier	**1**	**1**	**IA**
b) Replacement or addition of a supplier	**1, 2, 3, 4**	**1, 2, 3**	**IA**
c) Any change to suppliers of spacer devices for metered dose inhalers			**II**
Conditions			
1. No deletion of packaging component or device.			
2. The qualitative and quantitative composition of the packaging components/device and design specifications remain the same.			
3. The specifications and quality control method are at least equivalent.			
4. The sterilisation method and conditions remain the same, if applicable.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).			
2. For devices for medicinal products for human use, proof of CE marking.			
3. Comparative table of current and proposed specifications, if applicable.			

B.II.f) Stability

B.II.f.1 Change in the shelf-life or storage conditions of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Reduction of the shelf life of the finished product			
1. As packaged for sale	1	1, 2, 3	IA_{IN}
2. After first opening	1	1, 2, 3	IA_{IN}
3. After dilution or reconstitution	1	1, 2, 3	IA_{IN}
b) Extension of the shelf life of the finished product			
1. As packaged for sale (supported by real time data)		1, 2, 3	IB
2. After first opening (supported by real time data)		1, 2, 3	IB
3. After dilution or reconstitution (supported by real time data)		1, 2, 3	IB
4. Extension of the shelf-life based on extrapolation of stability data not in accordance with ICH/VICH guidelines*			II
5. Extension of the shelf-life of a biological/ immunological medicinal product in accordance with an approved stability protocol.		1, 2, 3	IB
c) Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol			II
d) Change in storage conditions of the finished product or the diluted/reconstituted product		1, 2, 3	IB
e) Change to an approved stability protocol	1, 2	1, 4	IA
Conditions			
1 The change should not be the result of unexpected events arising during manufacture or because of stability concerns unless the supporting documentation has been already assessed and approved within another procedure.			
2. The change does not concern a widening of the acceptance criteria in the parameters tested, a removal of stability indicating parameters or a reduction in the frequency of testing.			
Documentation			

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Conditions ... [11]

1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate). This must contain results of appropriate real time stability studies (covering the entire shelf life) conducted in accordance with the relevant stability guidelines on at least two pilot scale batches[1] of the finished product in the authorised packaging material and/or after first opening or reconstitution, as appropriate; where applicable, results of appropriate microbiological testing should be included. [1]Pilot scale batches can be accepted with a commitment to verify the shelf life on production scale batches.
2.	Revised product information.
3.	Copy of approved end of shelf life finished product specification and where applicable, specifications after dilution/reconstitution or first opening.
4.	Justification for the proposed change(s).
**Note: extrapolation not applicable for biological/immunological medicinal product*	

B.II.g) Design Space

B.II.g.1 Introduction of a new design space or extension of an approved design space for the finished product, concerning	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) One or more unit operations in the manufacturing process of the finished product including the resulting in-process controls and/or test procedures		**1, 2, 3**	**II**
b) Test procedures for excipients / intermediates and/or the finished product		**1, 2, 3**	**II**
Documentation			
1. Results from product and process development studies (including risk assessment and multivariate studies, as appropriate) demonstrating that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the finished product has been achieved.			
2. Description of the design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.			
3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).			

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B.II.h) Post approval change management protocols

B.II.h.1 Introduction of a post approval change management protocol related to the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
		1, 2, 3	**II**
Documentation			
1. Detailed description for the proposed change.			
2. Change management protocol related to the finished product			
3. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).			

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Conditions to be fulfilled ... [12]

B.II.h.2 Deletion of an approved change management protocol related to the finished product	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	1, 2	IA_{IN}

Conditions	
1.	The deletion of the approved change management protocol related to the finish product is not a result of unexpected events or out of specification results during the implementation of the change (s) described in the protocol.
Documentation	
1.	Justification for the proposed deletion.
2.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).

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Conditions to be fulfilled ... [13]

B.II.h.3 Changes to an approved post approval change management protocol related to the finished product		**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a	**Major changes to an approved post approval change management protocol**			**II**
b	**Minor changes to an approved post approval change management protocol that do not change the strategy defined in the protocol**		**1**	**IB**
Documentation				
1	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.			

B.II.h.4 Implementation of changes foreseen in an approved change management protocol related to the finished product		**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a)	**The implementation of the change requires no further supportive data and should be notified immediately to the competent authorities**	**1**	**1, 2, 4**	**IA_{IN}**
b)	**The implementation of the change requires no further supportive data and should be notified to the competent authorities within 12 months of implementation**	**1**	**1, 2, 4**	**IA**
c)	**The implementation of the change requires further supportive data**		**1, 2, 3, 4**	**IB**

	d) Implementation of a change for a biological/immunological medicinal product		**1, 2, 3, 4, 5**	**IB**
	Conditions			
	1. The proposed change has been performed fully in line with the approved change management protocol.			
	Documentation			
	1. Reference to the approved change management protocol.			
	2. Declaration that the change is in accordance with the approved change management protocol* and that the study results meet the acceptance criteria specified in the protocol. In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products.			
	3. Results of the studies performed in accordance with the approved change management protocol.			
	4. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).			
	5. Copy of approved specifications of the finished product.			
Note: Minor changes to a protocol to reflect the use of any updated analytical tests and limits, which have been formally registered and where relevant assessed and approved, will be acceptable at the time of implementation provided that they do not change the strategy defined in the protocol.				

B.II.i Adventitious Agents Safety

B.II.i.1 Update to the "Adventitious Agents Safety Evaluation" information (section 3.2.A.2)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Studies related to manufacturing steps investigated for the first time for one or more adventitious agents			II
b) Replacement of obsolete studies related to manufacturing steps and adventitious agents already reported in the dossier			
1) with modification of risk assessment			II
2) without modification of risk assessment		1, 2, 3	IB
Documentation			
1. Amendment of the relevant section(s) of the dossiers including the introduction of the new studies to investigate the capability of manufacturing steps to inactivate/reduce adventitious agents.			
2. Justification that the studies do not modify the risk assessment.			
3. Amendment of product information (where applicable).			

B.III CEP/TSE/MONOGRAPHS

B.III.1 Submission of a new or updated Ph. Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability: For an active substance For a starting material/reagent/intermediate used in the manufacturing process of the active substance For an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph.			
1. New certificate from an already approved manufacturer	1, 2, 3, 4, 5, 8, 11	1, 2, 3, 4, 5	IA_{IN}
2. Updated certificate from an already approved manufacturer (no new manufacturing site)	1, 2, 3, 4, 8	1, 2, 3, 4,	IA
3. New certificate from a new manufacturer (replacement or addition)	1, 2, 3, 4, 5, 8, 11	1, 2, 3, 4, 5	IA_{IN}
4. Updated certificate from an already approved manufacturer (includes new manufacturing site)	1, 2, 3, 4, 8	1, 2, 3, 4, 5	IA_{IN}
5. Deletion of certificates (in case multiple certificates exist per material)	10	3	IA
6. 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, 6	IB
b) European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient			
1. New certificate for an active substance from a new or an already approved manufacturer	3, 5, 6, 11	1, 2, 3, 4, 5	IA_{IN}
2. New certificate for a starting material/reagent/ intermediate/or excipient from a new or an already approved manufacturer	3, 6, 9	1, 2, 3, 4, 5	IA
3. Updated certificate from an already approved manufacturer	7, 9	1, 2, 3, 4, 5	IA
4. Deletion of certificates (in case multiple certificates exist per material)	10	3	IA

	5. New/updated certificate from an already-approved/new manufacturer using materials of human or animal origin for which an assessment of the risk with respect to potential contamination with adventitious agents is required			**II**

Conditions

1.	The finished product release and end of shelf life specifications remain the same.
2.	Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and product specific requirements (e.g. particle size profiles, polymorphic form), if applicable.
3.	The manufacturing process of the active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required.
4.	For active substance only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier.
5.	The active substance/starting material/reagent/intermediate/excipient is not sterile.
6.	The substance is not included in a veterinary medicinal product for use in animal species susceptible to TSE.
7.	For veterinary medicinal products: there has been no change in the source of material.
8.	For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.
9	If Gelatin is to be used in a medicinal product that is for parenteral use, if manufactured from bones, it should **only** be manufactured in compliance country requirements as stated in the Note for Guidance for minimising the risk transmitting animal spongiform encephalopathy (EMA/410/01 current revision).
10.	At least one manufacturer for the same substance remains in the dossier.
11.	If the active substance is a not a sterile substance but is to be used in a sterile medicinal product then according to the CEP it must not use water during the last steps of the synthesis or if it does the active substance must also be claimed to be free from bacterial endotoxins.

Documentation

1.	Copy of the proposed Ph. Eur. Certificate of Suitability.
2.	In case of an addition of a manufacturing site, the variation application form should clearly outline the "present" and "proposed" manufacturers as listed in section 2.5 of the application form for marketing authorisation.

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Documentation ... [14]

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3.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format.
4.	Where applicable, a document providing information of any materials falling within the scope of the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* including those which are used in the manufacture of the active substance/ excipient. The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use. For the Centralised Procedure, this information should be included in an updated TSE table A (and B, if relevant).
5.	Where applicable, for active substance - a declaration by the Qualified Person (QP) of each of the manufacturing authorisation holders listed in the application where the active substance is used as a starting material and a declaration by the QP of each of the manufacturing authorisation holders listed in the application as responsible for batch release. These declarations should state that the active substance manufacturer(s) referred to in the application operate in compliance with the detailed guidelines on good manufacturing practice for starting materials. A single declaration may be acceptable under certain circumstances - see the note under variation no. B.II.b.1. The manufacture of intermediates also require a QP declaration, while as far as any updates to certificates for active substances and intermediates are concerned, a QP declaration is only required if, compared to the previously registered version of the certificate, there is a change to the actual listed manufacturing sites.
6.	Suitable evidence to confirm that the water used in the final steps of the synthesis of the active substance complies with NfG on quality of water for pharmaceutical use (CPMP/QWP/158/01 Rev or EMEA/CVMP/115/01 Rev).

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

		specification need to correspond to the pharmacopoeial standard after the change, except any additional supplementary tests.
	2.	Additional specifications to the pharmacopoeia for product specific properties are unchanged (e.g. particle size profiles, polymorphic form or e.g. bioassays, aggregates).
	3.	No significant changes in qualitative and quantitative impurities profile unless the specifications are tightened
	4.	Additional validation of a new or changed pharmacopoeial method is not required
	5.	For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.
	Documentation	
	1.	Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate).
	2.	Comparative table of current and proposed specifications.
	3.	Batch analysis data (in a comparative tabulated format) on two production batches of the relevant substance for all tests in the new specification and additionally, where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch.. For herbal medicinal products, comparative disintegration data may be acceptable.
	4.	Data to demonstrate the suitability of the monograph to control the substance, e.g. a comparison of the potential impurities with the transparency note of the monograph.
	5.	A copy of the Ph.Eur. monograph /Member State national pharmacopoeia monograph for the concerned material as appropriate.
Note: There is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that compliance with the updated monograph is implemented within six months of its publication and reference is made to the 'current edition' in the dossier of an authorised medicinal product.		

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Supprimé: Where appropriate, batch analysis data (in a comparative tabulated format) on two production batches

Administrator

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

B.IV Medical Devices

B.IV.1 Change of a measuring or administration device	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Addition or replacement of a device which is not an integrated part of the primary packaging			
1. Device with CE marking	**1, 2, 3, 6, 7**	**1, 2, 4**	**IA_{IN}**
2. Device without CE marking for veterinary products only		**1, 3, 4**	**IB**
3. Spacer device for metered dose inhalers or other device which may have a significant impact on the delivery of the active substance in the product (e.g. nebuliser)			**II**
b) Deletion of a device	**4, 5**	**1, 5**	**IA_{IN}**
c) Addition or replacement of a device which is an integrated part of the primary packaging			**II**

Conditions

1. The proposed measuring or administration device must accurately deliver the required dose for the product concerned in line with the approved posology and results of such studies should be available.
2. The new device is compatible with the medicinal product.
3. The change should not lead to substantial amendments of the product information.
4. The medicinal product can still be accurately delivered.
5. For veterinary medicinal products, the device is not crucial for the safety of the person administering the product.
6. The proposed device presentation is not intended to be a solvent for the finished product.
7. If a measuring function is intended the CE marking should cover the measuring function.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including description, detailed drawing and composition of the device material and supplier where appropriate, and including revised product information as appropriate.
2. Proof of CE marking and if a measuring function is intended the proof of CE marking should also include the 4 digit notified body number.
3. Data to demonstrate accuracy, precision and compatibility of the device.

4.	Samples of the new device where applicable (see NTA, Requirements for samples in the Member States).
5.	Justification for the deletion of the device.

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

Administrator

Supprimé: Note: For B.IV.1.c), applicants are reminded that any change which results in a "new pharmaceutical form" requires the submission of an Extension application. ... [15]

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

Conditions

1.	The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure) unless the supporting documentation has been already assessed and approved within another procedure.
2.	The change should not be the result of unexpected events arising during manufacture.
3.	Any change should be within the range of currently approved limits.
4.	The test procedure remains the same.
5.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.

Documentation

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

2.	Comparative table of current and proposed specifications.
3.	Details of any new analytical method and summary of validation data.
4.	Batch analysis data on two production batches for all tests in the new specification.
5.	Either a declaration from the marketing authorisation holder that the parameter is non-significant based on a previously approved risk assessment, or a justification that it is obsolete
6.	Justification for the new specification parameter and the limits.

Administrator
Supprimé: Justification/risk-assessment showing

B.IV.3 Change in test procedure of a measuring or administration device for veterinary medicinal products	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Minor change to an approved test procedure	**1, 2**	**1, 2**	**IA**
b) Other changes to a test procedure (including replacement or addition)	**1, 3**	**1, 2**	**IA**
c) Deletion of a test procedure if an alternative test procedure is already authorised	**4**	**1**	**IA**

Conditions

1.	Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure.
2.	The method of analysis should remain the same.
3.	Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way
4.	An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA (IN) notification.

Documentation

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

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

B.V.a) PMF/VAMF

B.V.a.1 Inclusion of a new, updated or amended Plasma Master File in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) First-time inclusion of a new Plasma Master File affecting the properties of the finished product			**II**
b) First-time inclusion of a new Plasma Master File not affecting the properties of the finished product		**1, 2, 3, 4**	**IB**
c) Inclusion of an updated/amended Plasma Master File when changes affect the properties of the finished product		**1, 2, 3, 4**	**IB**
d) Inclusion of an updated/amended Plasma Master File when changes do not affect the properties of the finished product	**1**	**1, 2, 3, 4**	**IA_{IN}**
Conditions			
1. The updated or amended Plasma Master File has been granted a certificate of compliance with legislation of the Union in accordance with Annex I of Directive 2001/83/EC.			
Documentation			
1. Declaration that the PMF Certificate and Evaluation Report are fully applicable for the authorised product, PMF holder has provided the PMF Certificate, Evaluation report and PMF dossier to the MAH (where the MAH is different to the PMF holder), the PMF Certificate and Evaluation Report replace the previous PMF documentation for this Marketing Authorisation.			
2. PMF Certificate and Evaluation Report.			
3. An expert statement outlining all the changes introduced with the certified PMF and evaluating their potential impact on the finished products including product specific risk assessments.			
4. The variation application form should clearly outline the “present” and “proposed” PMF EMA Certificate (code number) in the MA dossier. When applicable, the variation application form should clearly list also all the other PMFs to which the medicinal product refers even if they are not the subject of the application.			

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

Conditions

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

Documentation

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

B.V.b) Referral

B.V.b.1 Update of the quality dossier following a Commission Decision following the procedure of Articles 30 or 31 of Directive 2001/83/EC or Articles 34 or 35 of Directive 2001/82/EC (referral procedure)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) The change implements the outcome of the referral*		**1, 2**	**IA_{IN}**
b) The harmonisation of the quality dossier was not part of the referral and the update is intended to harmonise it			**II**
Documentation			
1. Attached to the cover letter of the variation application: A reference to the Commission Decision concerned.			
2. The changes introduced during the referral procedure should be clearly highlighted in the submission.			
**Note: Applies in cases where the marketing authorisation holder(s) need to take steps to allow the Member States to comply with the Commission decision within 30 days after its notification in accordance with Article 34(3) of Directive 2001/83/EC and Article 38(3) of Directive 2001/82/EC.*			

C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES

C.I HUMAN AND VETERINARY MEDICINAL PRODUCTS

C.I.1 Change in the Summary of Product Characteristics, Labelling or Package Leaflet following a procedure in accordance with Articles 30, 31, 107g, 107k or 107q of Directive 2001/83/EC or Articles 34 or 35 of Directive 2001/82/EC or Article 29 of Regulation (EC) No. 1901/2006	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The medicinal product is covered by the defined scope of the procedure*		1, 2, 3	IA_{IN}
b) The medicinal product is not covered by the defined scope of the procedure but the change implements the outcome of the procedure and no new additional data are submitted by the MAH		1, 2, 3	IB
c) The medicinal product is not covered by the defined scope of the procedure but the change implements the outcome of the procedure with new additional data submitted by the MAH		1, 3	II

Documentation

1. Attached to the cover letter of the variation application: A reference to the Commission Decision concerned or to the agreement reached by the CMDh (as applicable) with the annexed Summary of Product Characteristics, Labelling or Package Leaflet.
2. A declaration that the proposed Summary of Product Characteristics, Labelling and Package Leaflet is identical for the concerned sections to that annexed to the Commission Decision on the procedure or to the agreement reached by the CMDh (as applicable).
3. Revised product information.

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

This variation covers implementation of conclusions of the assessment and recommendations made public in accordance with Article 23(3) of Directive 2001/83/EC and Article 16(3) of Regulation (EC) No 726/2004.

C.I.2 Change in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following	Conditions to be fulfilled	Documentation to be supplied	Procedure type

Administrator
Supprimé: B.V.c) Change management protocol

Administrator
Supprimé: B.V.c.1 Update of the quality dossier to implement changes, requested by the EMEA/National Competent Authority, following assessment of a change management prot ... [16]

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Administrator
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assessment of the same change for the reference product.			
a) Implementation of change(s) for which no new additional data are submitted by the MAH		**1, 2**	**IB**
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH (e.g. comparability)			**II**
Documentation			
1. Attached to the cover letter of the variation application: EMEA/NCA request, if applicable.			
2. Revised product information.			

C.I.3 Implementation of change(s) requested by the EMA/ National Competent Authority following the assessment of an Urgent Safety Restriction, class labelling, a Periodic Safety Update report(*), Risk Management Plan, Post-Authorisation Measure/Specific Obligation, data submitted under Article 45/46 of Regulation (EC) No 1901/2006, or amendments to reflect a competent authority Core SPC	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH		**1, 2**	**IB**
b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH		**1,2**	**II**
Documentation			
1. Attached to the cover letter of the variation application: EMA/NCA request with attached relevant assessment report, if available.			
2. Revised product information.			
Note: MAHs are reminded that once new information becomes available which might entail the variation of the MA, this should be submitted forthwith as a variation to the competent authorities, rather than awaiting the assessment of those data through one of the procedures mentioned above. This variation covers implementation of conclusions of the assessment and recommendations made public in accordance with Article 23(3) of Directive 2001/83/EC and Article 16(3) of Regulation (EC) No 726/2004. (*) This variation does not apply to implementation of changes following the assessment of a Periodic Safety Update report carried out in accordance with procedures Art 107e to 107g of			

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	Directive 2001/83/EC and Art 28 of Regulation (EC) No 726/2004

C.I.4 Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	Conditions to be fulfilled	Documentation to be supplied	Procedure type
			II
Note: This variation applies also for the submission of results of studies performed in compliance with a Paediatric Investigation Plan which do not support a paediatric indication.			

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

C.I.6 Change(s) to therapeutic indication(s)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Addition of a new therapeutic indication or modification of an approved one			II
b) Deletion of a therapeutic indication			IB
Note: Where the addition or modification of a therapeutic indication takes place in the context of the implementation of the outcome of a referral procedure or of changes to the product information of a generic/hybrid/biosimilar product following assessment of the same change for the reference product, variations C.I.1 and C.I.2 apply, respectively.			

C.I.7 Deletion of:	Conditions to	Documentation	Procedure

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

C.I.8 Introduction or changes to a summary of pharmacovigilance system for medicinal products for human use*	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Introduction of a summary of the pharmacovigilance system	**1, 2**	**1, 2, 3**	**IA_{IN}**
b) Changes in QPPV (including contact details) and/or changes in the PSMF location	**1,2,~~3~~**	**1, 2, and/or 3**	**IA_{IN}**
Conditions			
1. The PSMF is permanently available for inspection and a copy of the PSMF will be provided to the national competent authorities/EMA within 7 days upon request. The PSMF is located either at the site in the Union where the main pharmacovigilance activities of the marketing authorisation holder are performed or at the site where the qualified person responsible for pharmacovigilance operates.			
2. The QPPV resides and operates in the Union.			
Documentation			
1. Summary of the pharmacovigilance system or update of the relevant elements: • Proof that the applicant has at his disposal a qualified person responsible for pharmacovigilance and a statement signed by the applicant to the effect that the applicant has the necessary means to fulfil the tasks and responsibilities listed in Title IX of Directive 2001/83/EC. • Contact details of the QPPV, Member States in which the QPPV resides and carries out his/her tasks			

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1. ... [17]

	• PSMF location
	2. Curriculum vitae of the QPPV.
	3. PSMF number**
*Note: For introduction of a new pharmacovigilance system for veterinary medicinal products, please refer to C.II.7 **The requirement for a PSMF number will be applicable once the IT system is in place at the EMA to provide a unique number to each PSMF. C.I.8 a) covers the first time introduction of a PSMF irrespective of whether or not the MA file contained a DDPS. C.I.8 b): Once the Article 57 database is functional, changes in QPPV, including contact details (telephone and fax numbers, postal address and email address) and changes to the address of the PSMF (street, city, postcode, country) may be updated in the Article 57 database only, without the need for a variation, provided that this is done immediately. Where reference is made to Article 57 database, Applicants/MAH are requested, at the time of introducing/varying the summary of the pharmacovigilance system, to include a reference for future updates to 'current version of the information, as included in the Article 57 database' in addition to providing the QPPV information and the PSMF location.	

C.I.9 Changes to an existing pharmacovigilance system as described in the DDPS	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) **Change in the QPPV and/or QPPV contact details and/or back-up procedure**	1	1	IA_{IN}
b) **Change(s) in the safety database and/or major contractual arrangements for the fulfilment of pharmacovigilance obligations, and/or change of the site undertaking pharmacovigilance activities)**	1, 2, 3	1	IA_{IN}
c) **Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system (e.g. change of the major storage/archiving location, administrative changes).**	1	1	IA
d) **Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH.**	4	1, 2	IA_{IN}

Conditions

1. The pharmacovigilance system itself remains unchanged

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2.	The database system has been validated (when applicable)
3.	Transfer of data from other database systems has been validated (when applicable).
4.	The same changes to the DDPS are introduced for all medicinal products of the same MAH (same final DDPS version)
Documentation	
1.	Latest version of the DDPS, and, where applicable, latest version of the product specific addendum. These should include for changes to the QPPV a) summary CV of the new QPPV, b) proof of QPPV EudraVigilance registration, and c) a new statement of the MAH and the QPPV regarding their availability and the means for notification of adverse reactions signed by the new QPPV and the MAH, and reflecting any other consequential changes, e.g. to the organisation chart. When the QPPV and /or QPPV contact details are not included in a DDPS or no DDPS exists, the submission of a revised DDPS version is not required and the application form is to be provided.
2.	Reference of the application/procedure and product in which the change(s) were accepted.
Note: C.I.9 covers changes to an existing pharmacovigilance system 1) for veterinary medicinal products and 2) for human medicinal products during the transitional period until the first time introduction of a PSMF. Note for d): The assessment of a DDPS submitted as part of a new MAA/Extension/Variation may give rise to changes at the request of the national competent authority/EMEA in this DDPS. Where this occurs, the same change(s) can be introduced to the DDPS in other marketing authorisations of the same MAH by submitting a (grouped) Type IA_{IN} variation.	

C.I.10 Changes to the conditions and/or obligations of the marketing authorisation due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
			II
Note: This variation covers the situation where the only change introduced concerns the conditions and/or obligations of the marketing authorisation, including the conditions and/or obligations of marketing authorisations under exceptional circumstances and conditional marketing authorisation.			

C.I.11 Change in the frequency and/or date of submission of periodic safety update reports (PSUR)	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	**1, 2**	**IA_{IN}**
Conditions			
1. The change in the frequency and/or date of submission of the PSUR has been agreed by the			

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3. ... [18]

	CHMP/CMDh, as set out in the list of Union reference dates	
	Documentation	
	1. Attached to the cover letter of the variation application: A reference to the agreement reached by the CHMP/CMDh	
	2. Revised frequency and/or date of submission of the PSUR. (For medicinal products authorised via the centralised procedure, the full set of annexes, including the revised Annex II should be provided)	
Note: This variation applies only when the PSUR cycle is specified in the marketing authorisation and where PSUR submission is required.		

C.I.12 Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1	1, 2	IA_{IN}
Conditions			
1. The medicinal product is included or removed from the list of medicinal products that are subject to additional monitoring (as applicable)			
Documentation			
1. Attached to the cover letter of the variation application: A reference to the list of medicinal products that are subject to additional monitoring			
2. Revised product information			
Note: This variation covers the situation where the inclusion or deletion of the black symbol and explanatory statements is not done as part of another regulatory procedure (e.g. renewal or variation procedure affecting the product information).			

C.II VETERINARY MEDICINAL PRODUCT – SPECIFIC CHANGES

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

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

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

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

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

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

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

C.II.7 Introduction of a new Pharmacovigilance system	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Which has not been assessed by the relevant national competent authority/EMA for another product of the same MAH			II
b) Which has been assessed by the relevant national competent authority/EMA for another product of the same MAH(*)		1, 2	IB

Documentation

1. The new Detailed Description of the Pharmacovigilance System (DDPS)
2. Reference to the application/procedure and product in which the DDPS was assessed previously

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

D. PMF/VAMF

D.1 Change in the name and/or address of the VAMF certificate holder	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA_{IN}
Conditions			
1. The VAMF certificate holder shall remain the same legal entity.			
Documentation			
1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.			

D.2 Change in the name and/or address of the PMF certificate holder	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA_{IN}
Conditions			
1. The PMF certificate holder shall remain the same legal entity.			
Documentation			
1. A formal document from a relevant official body (e.g. Chamber of Commerce) in which the new name or new address is mentioned.			

D.3 Change or transfer of the current PMF certificate holder to a new PMF certificate holder -i.e. different legal entity-	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2, 3, 4, 5, 6	IA_{IN}
Documentation			
1. A document including the identification (name and address) of the current PMF Holder (transferor) and the identification (name and address) of the person to whom the transfer is to be granted (transferee) together with the proposed implementation date – signed by both companies.			
2. Copy of the latest PMF Certificate page 'EMEA Plasma Master File (PMF) Certificate of			

	compliance with Community legislation'.
3.	Proof of establishment of the new holder (Excerpt of the commercial register and the English translation of it) - signed by both companies.
4.	Confirmation of the transfer of the complete PMF documentation since the initial PMF certification to the transferee - signed by both companies.
5.	Letter of Authorisation including contact details of the person responsible for communication between the competent authority and the PMF holder - signed by the transferee.
6.	Letter of Undertaking to fulfil all open and remaining commitments (if any) - signed by the transferee.

D.4 Change in the name and/or address of a blood establishment including blood/plasma collection centres	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1, 2	1, 2, 3	IA
Conditions			
1. The blood establishment shall remain the same legal entity.			
2. The change shall be administrative (e.g. merger, take over); change in the name of the blood establishment/ collection centre provided the blood establishment shall remain the same.			
Documentation			
1. Signed declaration that the change does not involve a change of the quality system within the blood establishment.			
2. Signed declaration that there is no change in the list of the collection centres.			
3. Updated relevant sections and annexes of the PMF dossier.			

D.5 Replacement or addition of a blood/plasma collection centre within a blood establishment already included in the PMF	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2, 3	IB
Documentation			
1. Epidemiological data for viral markers related to the blood/plasma collection centre covering the last 3 years. For newly opened centre(s) or in case no data are yet available, a declaration that epidemiological data will be provided at the time of the next annual update(s).			
2. Statement that the centre is working under the same conditions as the other centres belonging to the blood establishment, as specified in the standard contract between blood establishment			

and PMF holder.
3. Updated relevant sections and annexes of the PMF dossier.

D.6 Deletion or change of status (operational/non-operational) of establishment(s)/centre(s) used for blood/plasma collection or in the testing of donations and plasma pools	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1, 2	1	IA
Conditions			
1. The reason for deletion or change of status should not be related to a GMP issue.			
2. The establishments(s)/centre(s) should comply with the legislation in terms of inspections in case of change of status from non-operational to operational.			
Documentation			
1. Updated relevant sections and annexes of the PMF dossier.			

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

D.8 Replacement or addition of a blood centre for testing of donations and/or plasma pools within an establishment already included in the PMF	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2	IB
Documentation			
1. Statement that the testing is performed following the same SOPs and/or test methods as already accepted.			
2. Updated relevant sections and annexes of the PMF dossier.			

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

D.10 Replacement or addition of a new blood establishment or centre(s) in which storage of plasma is carried out	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1, 2	IB
Documentation			
1. Statement that the storage centre is working following the same SOPs as the already accepted establishment.			
2. Updated relevant sections and annexes of the PMF dossier.			

D.11 Deletion of a blood establishment or centre(s) in which storage of plasma is carried out	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA
Conditions			
1. The reason for deletion should not be related to a GMP issues.			
Documentation			
1. Updated relevant sections and annexes of the PMF dossier.			

D.12 Replacement or addition of an organisation involved in the transport of plasma.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
		1	IB
Documentation			
1. Updated relevant sections and annexes of the PMF dossier, including a list of all the blood establishments using this transport organisation, a summary of the system in place to ensure that the transport is performed under appropriate conditions (time, temperature and GMP compliance) and confirmation that transport conditions are validated.			

D.13 Deletion of an organisation involved in the transport of plasma	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA
Conditions			
1. The reason for deletion should not be related to GMP issues.			

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

D.14 Addition of a CE-marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1, 2	IA
Conditions			
1. The new test kit is CE-marked.			
Documentation			
1. List of testing site(s) where the kit is used.			
2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing as requested in the "Guideline on the scientific data requirements for a PMF".			

D.15 Addition of a non-CE marked test kit to test individual donations as a new test kit or as a replacement of an existing test kit	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The new test kit has not previously been approved in the PMF for any blood centre for testing of donations			II
b) The new test kit has been approved in the PMF for other blood centre(s) for testing of donations		1, 2	IA
Documentation			
1. List of testing centre(s) where the kit is currently used and a list of testing centre(s) where the kit will be used.			
2. Updated relevant sections and annexes of the PMF dossier, including updated information on testing as requested in the "Guideline on the scientific data requirements for a PMF".			

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

D.17 Introduction or extension of inventory hold procedure.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1	IA
Conditions			
1. The inventory hold procedure is a more stringent procedure (e.g. release only after retesting of donors).			
Documentation			
1. Updated relevant sections of the PMF dossier, including the rationale for introduction or extension of inventory hold period, the sites where the inventory hold takes place and for changes to procedure, a decision tree including new conditions.			

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

Documentation
1. Updated relevant sections of the PMF dossier

D.19 Replacement or addition of blood containers (e.g. bags, bottles)	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) The new blood containers are CE-marked	1, 2	1	IA
b) The new blood containers are not CE-marked			II
Conditions			
1. The container is CE-marked.			
2. The quality criteria of the blood in the container remain unchanged.			
Documentation			
1. Updated relevant sections and annexes of the PMF dossier, including the name of container, manufacturer, anticoagulant solution specification, confirmation of CE-mark and the name of the blood establishments where the container is used.			

D.20 Change in storage / transport	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) storage and/or transport conditions	1	1	IA
b) maximum storage time for the plasma	1, 2	1	IA
Conditions			
1. The change should tighten the conditions and be in compliance with Ph. Eur. requirements for Human Plasma for Fractionation.			
2. The maximum storage time is shorter than previously.			
Documentation			
1. Updated relevant sections and annexes of the PMF dossier, including detailed description of the new conditions, confirmation of validation of storage/transport conditions and the name of the blood establishment(s) where the change takes place (if relevant).			

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

			II

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

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