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Committee for Medicinal Products for Veterinary Use

Advice on implementing measures under Article 60(1) of Regulation (EU) 2019/6 on veterinary medicinal products - Scientific recommendation on the list of variations not requiring assessment

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Introduction:

On 6 February 2019 the European Commission sent a request to the European Medicines Agency for scientific recommendations on the list of variations not requiring assessment, taking into account:

- the criteria listed in Article 60(2) of Regulation (EU) 2019/6:
    - the need for a scientific assessment of changes in order to determine the risk to public and animal health or to the environment;
    - whether changes have an impact on quality, safety or efficacy of the veterinary medicinal product;
    - whether changes imply no more than a minor alteration of the summary of product characteristics;
    - whether changes are of an administrative nature.
- the experience gained with the application of the current system as established in Commission Regulation (EC) No 1234/2008 and the accompanying 'Guidelines on the details of various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures (2012/C/223/01)'.

The Committee for Medicinal Products for Veterinary Use (CVMP) formed an expert group to prepare this list of variations not requiring assessment and make the recommendations. The group was composed of five experts selected from the European network of experts, on the basis of recommendations from the national competent authorities and, two Agency staff members with experience with variations for chemical and biological products and with one member having experience with variations for medicinal products for human use.

Considering the relevance of the advice to marketing authorisations approved through decentralised, mutual recognition and national procedures, the CVMP expert group received and carefully considered the significant contribution from the Coordination Group for mutual recognition and decentralised procedures - veterinary (CMDv).

The contribution from the CMDv was submitted to CVMP on 29 March 2019. Following review of the CMDv proposals the expert group submitted their draft list to the CVMP on 29 May 2019.

The CVMP adopted the scientific recommendation on 18 July 2019.

Considerations and rationale for the list of variations not requiring assessment

Regulation (EU) 2019/6 aims to reduce the administrative burden, enhance the internal market and increase the availability of veterinary medicinal products, while guaranteeing the highest level of public and animal health and environmental protection.

Simplification of the procedures for variations of existing marketing authorisations is one of the aspects considered as part of the objective of reducing administrative burden.

Article 60(1) of Regulation (EU) 2019/6 states that the European Commission shall, by means of implementing acts, establish a list of variations to marketing authorisations of veterinary medicinal products that do not require assessment.

For the preparation of the recommendation, all variations listed in the current Classification Guidance on minor variations of type 1A minor variations of Type 1B and major variations of Type II (Classification Guideline) and all CMDh and CMDv recommendations for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008, were considered. Additional categories of variations elucidated in the CMDh/CMDv questions and answers document, Q&A- List for the submission of variations according to Commission Regulation (EC) No 1234/2008, have also been examined.

Each variation was considered in the context of products that have either a chemical or biological active substance.

Variations concerning pharmacovigilance were also factored in based on the current practices but will need to be revisited once the Implementing Act on measures on good pharmacovigilance practice defining a new pharmacovigilance system is adopted.

It is acknowledged that the practical management of variations not requiring assessment will depend on the functionality of the Union Product Database (UPD) for veterinary medicinal products, which should be established according to Article 55 of Regulation (EU) 2019/6.

Recommendations

The list of variations that do not require assessment was prepared according to the criteria in Article 60(2) of Regulation (EU) 2019/6 and in fulfillment of the mandate to provide a scientific recommendation. Nearly all type IA and IA_{IN} variations and a number of type IB variations that are listed in the current variations Classification Guideline are recommended to be classified as not requiring assessment. Following extensive discussions, which took into account assessment experience and experience with the current Classification Guideline, it was not considered that any current type II variation warrants inclusion on the list of variations not requiring assessment.

The current requirements for conditions and documentation in the variations Classification Guideline should be retained for all assessed and non-assessed variations with new and revised conditions for the type IB variations, which are now classified as not requiring assessment, being introduced. The wording of conditions and documentation requirements for some of the former type IA/IA_{IN} notifications should be clarified for ease of use.

Assuming that a recommendation process for classification similar to the existing one for unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008 will be retained, it is proposed that a number of overarching variations be included (see table) to enable flexibility with respect to unforeseen variations.

The list of variations not requiring assessment is presented in the attached table and contains the description, subcategory, and classification (type IA, IA_{IN} etc.) of the variations as they are listed in the current variations Classification Guideline. The list also includes all CMDh and CMDv recommendations for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008 and some more variations set down in the CMDh/CMDv questions and answers document, Q&A- List for the submission of variations according to Commission Regulation

(EC) No 1234/2008. Proposed new variation categories, which are not in the variation classification guideline, have been included in the proposed list and are written in red. The recommendation on the new classification (assessment not required) for products that have either a chemical or a biological active substance is captured in two columns, 'Scientific Recommendation Non-Biologicals and 'Scientific Recommendation Biologicals/Immunologicals'. In these columns the entry "Yes" formatted in light green means that the specific variation can be a variation not requiring assessment. In some instances, the variation will only be considered a "Yes" for either the non-biological or the biological/immunological product. These instances have been reflected with the entry of either an "n.a." to indicate that the variation does not apply to that product type, or with the entry of a "No" formatted in red to indicate that assessment is required for that product type.

The last column indicates the variations where conditions apply and/or documentation is required to approve the variation.

Additional recommendations and points to note

Upon application of the Implementing Act the common (human and veterinary) variations Classification Guideline for medicinal products for human use and veterinary medicinal products will cease to be valid for veterinary medicines. However, as there is extensive experience with the existing variation code system and its conditions and documentation requirements, it is recommended that the same variation code system is maintained. These variation codes indicate at a high level the changes being applied for and can be easily displayed in currently utilised IT systems and potentially be effortlessly transferred from system to system. Consequently, it is recommended that a specific veterinary variation guidance similar to the current variations Classification Guideline is developed before Regulation (EU) 2019/6 enters into force (28 January 2022). The unforeseen variations should be included in the future veterinary variations guidance and be assigned new variation codes. When drafting the Implementing Act this should also be taken into account. The veterinary variations guidance should also list the conditions and document requirements (if any) that should be met for each variation. In addition, noting that Article 66 only requires completion of procedures within 60 days, it is also recommended that the level of complexity of a variation requiring assessment be reflected in the assessment timetable with a shorter timetable for less complex variations. It is recommended that mechanisms are put in place to approve and conclude procedures before the procedure end date if appropriate.

Finally, in addition to providing the mandated list of variations that do not require assessment, the practical application of this list for both applicants and National Competent Authorities has been considered. It is important to note that the regulatory approval of many variations on the list of variations not requiring assessment is dependent on the UPD having at least the range of functions specified in Regulation (EU) 2019/6 and the implementing act specified under Article 55 (3). These variations require a mechanism to allow provision of documentation during the procedure and a way of handling variations in the UPD which does not change any values in data fields or the SPC and product literature or else it may not be possible for these procedures to be handled exclusively through the UPD. The documentation relevant to the variation submitted for approval is needed to facilitate regulatory oversight and to accurately determine, at a point in time, the regulatory compliance with conditions under which a given product is authorised.

Concluding remarks

The proposed list of variations not requiring assessment will further simplify current arrangements and reduce administrative burden by classifying 25% (chemical) and 19.7% (biological) of the current type IB variations as not requiring assessment. Additionally, in total 51.3% of all applicable variations for

chemicals have been classified as not requiring assessment compared to 46.5% type IA/IA_{IN} notifications in the current system. For biologicals 47.5% of all applicable variations have been classified as not requiring assessment compared to 43.1% type IA/IA_{IN} notifications in the current system. This reduction in the number of variations to be assessed will lead to an overall reduction of burden when processing variations.

Table: List of variations for non-biological, biological and immunological veterinary medicinal products that do not require scientific assessment.

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
A.z (04.04.2016) Change in the nomenclature of the container material for immediate packaging of the finished product.		**IA**	Yes	Yes	Yes
A.1 Change in the name and/or address of the marketing authorisation holder		**IA_{IN}**	Yes	Yes	Yes
A.2 Change in the (invented) name of the medicinal product	a) for centrally authorised products	**IA_{IN}**	Yes	Yes	Yes
A.3 Change in name of the active substance or of an excipient		**IA_{IN}**	Yes	Yes	Yes
A.4 Change in the name and/or address of: a manufacturer (including where relevant quality control testing sites);-or a supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the technical dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier; or a manufacturer of a novel excipient (where specified in the technical dossier)		**IA**	Yes	Yes	Yes
A.4 Change in the name and/or address of: an Active Substance Master File ASMF holder;		**IA**	Yes	Yes	Yes
A.5 Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites)	a) The activities for which the manufacturer/importer is responsible include batch release	**IA_{IN}**	Yes	Yes	Yes
A.5 Change in the name and/or address of a manufacturer/importer of the finished product (including batch release or quality control testing sites)	b) The activities for which the manufacturer/importer is responsible do not include batch release	**IA**	Yes	Yes	Yes
A.6 Change in ATC Code / ATC Vet Code		**IA**	Yes	Yes	Yes
A.7 Deletion of manufacturing sites for an active substance, intermediate or finished product,		**IA**	Yes	Yes	Yes

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
packaging site, manufacturer responsible for batch release, site where batch control takes place, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)					
A.8 Changes to date of the audit to verify GMP compliance of the manufacturer of the active substance		**IA**	Yes	Yes	Yes
B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	**IA_{IN}**	Yes	n.a.	Yes
B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	f) Changes to quality control testing arrangements for the active substance- replacement or addition of a site where batch control/testing takes place	**IA**	Yes	n.a.	Yes
B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	i) Introduction of a new site of micronisation	**IA**	Yes	n.a.	Yes
B.I.a.1 Change in the manufacturer of a starting material/reagent/intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	k) New storage site of Master Cell Bank and/or Working Cell Banks	**IB**	Yes	Yes	Yes
B.I.a.2 Changes in the manufacturing process of the	a) Minor change in the manufacturing process	**IA**	Yes	n.a.	Yes

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
active substance	of the active substance				
B.I.a.2 Changes in the manufacturing process of the active substance	z) (17.12.12) Deletion of one manufacturing process of the drug substance manufacturing processes	**IA**	Yes	Yes	Yes
B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance	a) Up to 10-fold increase compared to the originally approved batch size	**IA**	Yes	n.a.	Yes
B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance	b) Downscaling down to 10-fold	**IA**	Yes	n.a.	Yes
B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate used in the manufacturing process of the active substance	d) More than 10-fold increase compared to the originally approved batch size	**IB**	yes	n.a.	Yes
B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance	a) Tightening of in-process limits	**IA**	Yes	Yes	Yes
B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance	b) Addition of a new in-process test and limits	**IA**	Yes	Yes	Yes
B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance	c) Deletion of a non-significant in-process test	**IA**	Yes	Yes	Yes
B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance	z) (09.04.13) Minor change of an analytical procedure for an in-process control.	**IA**	Yes	Yes	Yes
B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance	a) Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release	**IA_{IN}**	n.a.	Yes	Yes
B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance	b) Tightening of specification limits	**IA**	Yes	Yes	Yes
B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance	c) Addition of a new specification parameter to the specification with its corresponding test method	**IA**	Yes	Yes	Yes

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance	d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**IA**	Yes	Yes	Yes
B.I.b.2 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance	a) Minor changes to an approved test procedure	**IA**	Yes	Yes	Yes
B.I.b.2 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance	b) Deletion of a test procedure for the active substance or a starting material/reagent/intermediate, if an alternative test procedure is already authorised.	**IA**	Yes	Yes	Yes
B.I.b.2 Change in test procedure for active substance or starting material/reagent/intermediate used in the manufacturing process of the active substance	c) Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance	**IA**	Yes	n.a.	Yes
B.I.c.1 Change in immediate packaging of the active substance	a) Qualitative and/or quantitative composition	**IA**	Yes	n.a.	Yes
B.I.c.1 Change in immediate packaging of the active substance	z) (14.12.2016) Deletion of one of the authorised bulk or final containers	**IA**	Yes	Yes	Yes
B.I.c.2 Change in the specification parameters and/or limits of the immediate packaging of the active substance	a) Tightening of specification limits	**IA**	Yes	Yes	Yes
B.I.c.2 Change in the specification parameters and/or limits of the immediate packaging of the active substance	b) Addition of a new specification parameter to the specification with its corresponding test method	**IA**	Yes	Yes	Yes
B.I.c.2 Change in the specification parameters and/or limits of the immediate packaging of the active substance	c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**IA**	Yes	Yes	Yes
B.I.c.3 Change in test procedure for the immediate packaging of the active substance	a) Minor changes to an approved test procedure	**IA**	Yes	Yes	Yes
B.I.c.3 Change in test procedure for the immediate	b) Other changes to a test procedure	**IA**	Yes	n.a.	Yes

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
packaging of the active substance	(including replacement or addition)				
B.I.c.3 Change in test procedure for the immediate packaging of the active substance	c) Deletion of a test procedure if an alternative test procedure is already authorised	**IA**	Yes	Yes	Yes
B.I.d.1 Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier	a) Re-test period/storage period 1. Reduction	**IA**	Yes	n.a.	Yes
B.I.d.1 Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier	b) Storage conditions 1. Change to more restrictive storage conditions of the active substance	**IA**	Yes	Yes	Yes
B.I.d.1 Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier	b) Storage conditions 1. Change to more restrictive storage conditions (28.06.10) Change in storage conditions of the reference standard. The same principles will apply as outlined for the active substance. of the active substance	**IA**	Yes	Yes	Yes
B.I.d.1 Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier	c) Change to an approved stability protocol	**IA**	Yes	Yes	Yes
B.I.e.3 Deletion of an approved change management protocol related to the active substance		**IA_{IN}**	Yes	Yes	Yes
B.I.e.4 Changes to an approved change management protocol	b) Minor changes to an approved change management protocol that do not change the strategy defined in the protocol	**IB**	Yes	Yes	Yes
B.I.e.5 Implementation of changes foreseen in an approved change management protocol	a) The implementation of the change requires no further supportive data	**IA_{IN}**	Yes	Yes	Yes
B.I.z Editorial changes to part 2 if inclusion in an upcoming procedure concerning part 2 is not possible			Yes	Yes	Yes
B.II.a.1 Change or addition of imprints, bossing or other markings including replacement, or addition	a) Changes in imprints, bossing or other markings	**IA_{IN}**	Yes	Yes	Yes

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
of inks used for product marking.					
B.II.a.2 Change in the shape or dimensions of the pharmaceutical form	a) Immediate release tablets, capsules, suppositories and pessaries	**IA_{IN}**	Yes	Yes	Yes
B.II.a.3 Changes in the composition (excipients) of the finished product	a) Changes in components of the flavouring or colouring system 2. Increase or reduction	**IA**	Yes	Yes	Yes
B.II.a.3 Changes in the composition (excipients) of the finished product	b) Other excipients 1. Any minor adjustment of the quantitative composition of the finished product with respect to excipients	**IA**	Yes	Yes	Yes
B.II.a.4 Change in coating weight of oral dosage forms or change in weight of capsule shells	a) Solid oral pharmaceutical forms	**IA**	Yes	Yes	Yes
B.II.a.6 Deletion of the solvent / diluent container from the pack		**IB**	Yes	Yes	Yes
B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	a) Secondary packaging site	**IA_{IN}**	Yes	Yes	Yes
B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	b) Primary packaging site	**IA_{IN}**	Yes	n.a.	Yes
B.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product	a) Replacement or addition of a site where batch control/testing takes place	**IA**	Yes	n.a.	Yes
B.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product	c) Replacement or addition of a manufacturer responsible for importation and/or batch release 1. Not including batch control/testing	**IA_{IN}**	Yes	Yes	Yes
B.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product	c) Replacement or addition of a manufacturer responsible for importation and/or batch release 2. Including batch control/testing	**IA_{IN}**	Yes	n.a.	Yes
B.II.b.3 Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product	a) Minor change in the manufacturing process	**IA**	Yes	Yes	Yes
B.II.b.3 Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product	z) (26.09.11) Change in the packaging material of bulk product not in contact with the bulk product formulation (including	**IA**	Yes	Yes	Yes

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
	replacement or addition)				
B.II.b.3 Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product	z) (27.02.2017) Deletion of one manufacturing process of the drug product manufacturing processes	**IA**	Yes	Yes	Yes
B.II.b.4 Change in the batch size (including batch size ranges) of the finished product	a) Up to 10-fold compared to the originally approved batch size	**IA**	Yes	n.a.	Yes
B.II.b.4 Change in the batch size (including batch size ranges) of the finished product	a) Up to 10-fold compared to the originally approved batch size (17.10.2016) Increase of the batch size up to 10-fold for the pharmaceutical form medicinal gas.	**IB**	Yes	Yes	Yes
B.II.b.4 Change in the batch size (including batch size ranges) of the finished product	b) Downscaling down to 10-fold	**IA**	Yes	n.a.	Yes
B.II.b.4 Change in the batch size (including batch size ranges) of the finished product	b) Downscaling down to 10-fold (17.10.2016) downscale of the batch size down to 10-fold for the pharmaceutical form medicinal gas.	**IB**	Yes	Yes	Yes
B.II.b.4 Change in the batch size (including batch size ranges) of the finished product	e) More than 10-fold increase compared to the originally approved batch size for immediate release (oral) pharmaceutical forms	**IB**	Yes	No	Yes
B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product	a) Tightening of in-process limits	**IA**	Yes	Yes	Yes
B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product	b) Addition of a new test(s) and limits	**IA**	Yes	Yes	Yes
B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product	c) Deletion of a non-significant in-process test	**IA**	Yes	Yes	Yes
B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product	z) (27.09.10) The in-process limits for hardness are proposed to be widened from 65-85 N to 45-85 N. The lower limits will be at 45N and therefore closer to the limits in the finished product specifications (25-85 N).	**IB**	Yes	n.a.	Yes
B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product	z) (25.03.13) Minor change of an analytical procedure for an in-process control	**IA**	Yes	Yes	Yes
B.II.c.1 Change in the specification parameters and/or limits of an excipient	a) Tightening of specification limits	**IA**	Yes	Yes	Yes

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
B.II.c.1 Change in the specification parameters and/or limits of an excipient	b) Addition of a new specification parameter to the specification with its corresponding test method	**IA**	Yes	Yes	Yes
B.II.c.1 Change in the specification parameters and/or limits of an excipient	c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**IA**	Yes	Yes	Yes
B.II.c.1 Change in the specification parameters and/or limits of an excipient	z) (25.07.11) Details on testing frequency for excipients are seen as a GMP issue, therefore all the detailed information on testing frequency for excipients in the chemical pharmaceutical dossier (Module 3) should be deleted via a Type IB variation	**IB**	Yes	Yes	Yes
B.II.c.2 Change in test procedure for an excipient	a) Minor changes to an approved test procedure	**IA**	Yes	Yes	Yes
B.II.c.2 Change in test procedure for an excipient	b) Deletion of a test procedure if an alternative test procedure is already authorised	**IA**	Yes	Yes	Yes
B.II.c.3 Change in source of an excipient or reagent with TSE risk	a) From TSE risk material to vegetable or synthetic origin 1. For excipients or reagents not used in the manufacture of a biological / immunological active substance or in a biological / immunological medicinal product	**IA**	Yes	n.a.	Yes
B.II.c.3 Change in source of an excipient or reagent with TSE risk	z) (17.12.12) Change in source of excipient unlikely to present any risk of TSE contamination	**IA**	Yes	Yes	Yes
B.II.c.4 Change in synthesis or recovery of a nonpharmacopoeial excipient (when described in the dossier) or a novel excipient	a) Minor change in synthesis or recovery of a nonpharmacopoeial excipient or a novel excipient	**IA**	Yes	Yes	Yes
B.II.d.1 Change in the specification parameters and/or limits of the finished product	a) Tightening of specification limits	**IA**	Yes	Yes	Yes
B.II.d.1 Change in the specification parameters and/or limits of the finished product	a) (20.12.10) Update of the dossier to comply with the provisions of a general monograph for the test of a finished product of the Ph.Eur. – Tightening of specification limits	**IA**	Yes	Yes	Yes

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
B.II.d.1 Change in the specification parameters and/or limits of the finished product	b) Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release	**IA_{IN}**	n.a.	Yes	Yes
B.II.d.1 Change in the specification parameters and/or limits of the finished product	c) Addition of a new specification parameter to the specification with its corresponding test method	**IA**	Yes	Yes	Yes
B.II.d.1 Change in the specification parameters and/or limits of the finished product	d) Deletion of 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)	**IA**	Yes	Yes	Yes
B.II.d.1 Change in the specification parameters and/or limits of the finished product	h) Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur for the finished product*	**IA_{IN}**	Yes	Yes	Yes
B.II.d.1 Change in the specification parameters and/or limits of the finished product	i) Ph. Eur. 2.9.40 Uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 (Uniformity of mass). or Ph. Eur. 2.9.6 (Uniformity of content)	**IA**	Yes	Yes	Yes
B.II.d.1 Change in the specification parameters and/or limits of the finished product	z) (30.04.14) The introduction of Ph. Eur. 2.9.6 “Uniformity of content of single-dose preparations” and/or Ph. Eur. 2.9.5 “Uniformity of mass of single-dose preparations”, as appropriate, to replace the currently registered Ph. Eur. 2.9.40 “Uniformity of dosage units (by CU)	**IA**	Yes	Yes	Yes
B.II.d.1 Change in the specification parameters and/or limits of the finished product	z) (20.12.10) Change in the specification parameters and/or limits of the finished product to more accurately describe the appearance of the drug product.	**IA**	Yes	Yes	Yes
B.II.d.2 Change in test procedure for the finished product	a) Minor changes to an approved test procedure	**IA**	Yes	Yes	Yes
B.II.d.2 Change in test procedure for the finished product	b) Deletion of a test procedure if an alternative method is already authorised	**IA**	Yes	Yes	Yes
B.II.d.2 Change in test procedure for the finished	e) Update of the test procedure to comply with	**IA**	Yes	Yes	Yes

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
product	the updated general monograph in the Ph. Eur.				
B.II.d.2 Change in test procedure for the finished product	f) To reflect compliance with the Ph.Eur. and remove reference to the outdated internal test method and test method number*	**IA**	Yes	Yes	Yes
B.II.e.1 Change in immediate packaging of the finished product	a) Qualitative and quantitative composition 1. Solid pharmaceutical forms	**IA**	Yes	No	Yes
B.II.e.1 Change in immediate packaging of the finished product	b) Change in type of container or addition of a new container 3. Deletion of an immediate packaging container that does not lead to the complete deletion of a strength or pharmaceutical form	**IA**	Yes	Yes	Yes
B.II.e.1 Change in immediate packaging of the finished product	z) (25.07.11) Details on testing frequency for packaging material are seen as a GMP issue, therefore all the detailed information on testing frequency for packaging material in the chemical pharmaceutical dossier (Module 3) should be deleted via a Type IB variation	**IB**	Yes	Yes	Yes
B.II.e.2 Change in the specification parameters and/or limits of the immediate packaging of the finished product	a) Tightening of specification limits	**IA**	Yes	Yes	Yes
B.II.e.2 Change in the specification parameters and/or limits of the immediate packaging of the finished product	b) Addition of a new specification parameter to the specification with its corresponding test method	**IA**	Yes	Yes	Yes
B.II.e.2 Change in the specification parameters and/or limits of the immediate packaging of the finished product	c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**IA**	Yes	Yes	Yes
B.II.e.3 Change in test procedure for the immediate packaging of the finished product	a) Minor changes to an approved test procedure	**IA**	Yes	Yes	Yes
B.II.e.3 Change in test procedure for the immediate packaging of the finished product	b) Other changes to a test procedure (including replacement or addition)	**IA**	Yes	n.a.	Yes
B.II.e.3 Change in test procedure for the immediate packaging of the finished product	c) Deletion of a test procedure if an alternative test procedure is already authorised	**IA**	Yes	Yes	Yes

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
B.II.e.4 Change in shape or dimensions of the container or closure (immediate packaging)	a) Non-sterile medicinal products	**IA**	Yes	Yes	Yes
B.II.e.5 Change in pack size of the finished product	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	**IA_{IN}**	Yes	Yes	Yes
B.II.e.5 Change in pack size of the finished product	b) Deletion of pack size(s)	**IA**	Yes	Yes	Yes
B.II.5.z	(30.06.2014) Addition of or change to a calendar package for a pack size already registered in the dossier.	**IA_{IN}**	Yes	Yes	Yes
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))	a) Change that affects the product information	**IA_{IN}**	Yes	Yes	Yes
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))	b) Change that does not affect the product information	**IA**	Yes	Yes	Yes
B.II.e.7 Change in supplier of packaging components or devices (when mentioned in the dossier)	a) Deletion of a supplier	**IA**	Yes	Yes	Yes
B.II.e.7 Change in supplier of packaging components or devices (when mentioned in the dossier)	a) (22.11.10) Change in the name of a supplier of a packaging component. If the information is not needed in the dossier CMDh recommends deletion of this information.	**IA**	Yes	Yes	Yes
B.II.e.7 Change in supplier of packaging components or devices (when mentioned in the dossier)	b) Replacement or addition of a supplier	**IA**	Yes	Yes	Yes
B.II.f.1 Change in the shelf-life or storage conditions of the finished product	a) Reduction of the shelf life of the finished product 1. As packaged for sale	**IA_{IN}**	Yes	Yes	Yes
B.II.f.1 Change in the shelf-life or storage conditions of the finished product	a) Reduction of the shelf life of the finished product 2. After first opening	**IA_{IN}**	Yes	Yes	Yes

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
B.II.f.1 Change in the shelf-life or storage conditions of the finished product	a) Reduction of the shelf life of the finished product 3. After dilution or reconstitution	**IA_{IN}**	Yes	Yes	Yes
B.II.f.1 Change in the shelf-life or storage conditions of the finished product	e) Change to an approved stability protocol	**IA**	Yes	Yes	Yes
B.II.g.3 Deletion of an approved change management protocol related to the finished product		**IA_{IN}**	Yes	Yes	Yes
B.II.g.4 Changes to an approved change management protocol	b) Minor changes to an approved change management protocol that do not change the strategy defined in the protocol	**IB**	Yes	Yes	Yes
B.II.g.5 Implementation of changes foreseen in an approved change management protocol	a) The implementation of the change requires no further supportive data	**IA_{IN}**	Yes	Yes	Yes
B.II.z Editorial changes to part 2 if inclusion in an upcoming procedure concerning part 2 is not possible			Yes	Yes	Yes
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	a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. 1. New certificate from an already approved manufacturer	**IA_{IN}**	Yes	Yes	Yes
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	a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. 2. Updated certificate from an already approved manufacturer	**IA**	Yes	Yes	Yes
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	a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. 3. New certificate from a new manufacturer (replacement or addition)	**IA_{IN}**	Yes	Yes	Yes

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
For an excipient					
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	a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph. 4. Deletion of certificates (in case multiple certificates exist per material)	**IA**	Yes	Yes	Yes
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	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	**IA_{IN}**	Yes	Yes	Yes
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	b) European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient 2. New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	**IA**	Yes	Yes	Yes
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	b) European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient 3. Updated certificate from an already approved manufacturer	**IA**	Yes	Yes	Yes
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	b) European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient 4. Deletion of certificates (in case multiple certificates exist per material)	**IA**	Yes	Yes	Yes

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State	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	**IA_{IN}**	Yes	Yes	Yes
B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State	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 2. Excipient/active substance starting material	**IA**	Yes	Yes	Yes
B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State	b) Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	**IA**	Yes	Yes	Yes
B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State	c) Change in specifications from a national pharmacopoeia of a Member State to the Ph. Eur.	**IA**	Yes	Yes	Yes
B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State	z) (23.05.11) To reflect compliance with the Ph.Eur. and remove reference to the internal test method and test method number.	**IA**	Yes	Yes	Yes
B.IV.1 Change of a measuring or administration device	a) Addition or replacement of a device which is not an integrated part of the primary packaging 1. Device with CE marking	**IA_{IN}**	Yes	Yes	Yes
B.IV.1 Change of a measuring or administration device	b) Deletion of a device	**IA_{IN}**	Yes	Yes	Yes
B.IV.2 Change in specification parameters and/or limits of a measuring or administration device for veterinary medicinal products	a) Tightening of specification limits	**IA**	Yes	Yes	Yes
B.IV.2 Change in specification parameters and/or limits of a measuring or administration device for veterinary medicinal products	b) Addition of a new specification parameter to the specification with its corresponding test method	**IA**	Yes	Yes	Yes
B.IV.2 Change in specification parameters and/or limits of a measuring or administration device for veterinary medicinal products	f) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**IA**	Yes	Yes	Yes
B.IV.3 Change in test procedure of a measuring or	a) Minor change to an approved test	**IA**	Yes	Yes	Yes

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
administration device for veterinary medicinal products	procedure				
B.IV.3 Change in test procedure of a measuring or administration device for veterinary medicinal products	b) Other changes to a test procedure (including replacement or addition)	**IA**	Yes	Yes	Yes
B.IV.3 Change in test procedure of a measuring or administration device for veterinary medicinal products	c) Deletion of a test procedure if an alternative test procedure is already authorised	**IA**	Yes	Yes	Yes
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)	c) Inclusion of an updated/amended Vaccine Antigen Master File, when changes do not affect the properties of the finished product	**IA_{IN}**	n.a.	Yes	Yes
B.V.b.1 Update of the quality dossier intended to implement the outcome of a Union referral procedure	a) The change implements the outcome of the referral	**IA_{IN}**	Yes	Yes	Yes
C.I.1 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure	a) The medicinal product is covered by the defined scope of the procedure	**IA_{IN}**	Yes	Yes	Yes
C.I.1 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet intended to implement the outcome of a Union referral procedure	b) The medicinal product is not covered by the defined scope of the procedure but the change(s) implements the outcome of the procedure and no new additional data is required to be submitted by the MAH	**IB**	Yes	Yes	Yes
C.I.2 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of a generic/hybrid/biosimilar medicinal products following assessment of the same change for the reference product	a) Implementation of change(s) for which no new additional data is required to be submitted by the MAH	**IB**	Yes	Yes	Yes
C.I.3 Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of human medicinal products intended to implement the outcome of a procedure concerning PSUR or PASS, or the outcome of the assessment done by the competent authority under Articles 45 or 46 of	a) Implementation of wording agreed by the competent authority	**IA_{IN}**	Yes	Yes	Yes

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
Regulation 1901/2006					
C.I.z Change(s) in the Summary of Product Characteristics, Labelling or Package Leaflet of veterinary medicinal products intended to implement recommendations from the competent authority or the Agency concerning risk management measures in pharmacovigilance related to veterinary medicinal products	a) Implementation of wording agreed and no new additional data / national translation are required to be submitted by the MAH		Yes	Yes	Yes
C.I.7 Deletion of a pharmaceutical form or strength	a) a pharmaceutical form	**IB**	Yes	Yes	Yes
C.I.7 Deletion of a pharmaceutical form or strength	b) a strength	**IB**	Yes	Yes	Yes
C.I.8 Introduction of, or changes to, a summary of pharmacovigilance system for medicinal products for human use	a) Introduction of a summary of pharmacovigilance system, changes in QPPV (including contact details) and/or changes in the Pharmacovigilance System Master File (PSMF) location	**IA_{IN}**	Yes	Yes	Yes
C.I.9 Change(s) to an existing pharmacovigilance system as described in the detailed description of the pharmacovigilance system (DDPS).	a) Change in the QPPV and/or QPPV contact details and/or back-up procedure	**IA_{IN}**	Yes	Yes	Yes
C.I.9 Change(s) to an existing pharmacovigilance system as described in the detailed description of the pharmacovigilance system (DDPS).	b) Change(s) in the safety database and/or major contractual arrangements for the fulfilment of pharmacovigilance obligations, and/or change of the site undergoing pharmacovigilance activities	**IA_{IN}**	Yes	Yes	Yes
C.I.9 Change(s) to an existing pharmacovigilance system as described in the detailed description of the pharmacovigilance system (DDPS).	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)	**IA**	Yes	Yes	Yes
C.I.9 Change(s) to an existing pharmacovigilance system as described in the detailed description of the pharmacovigilance system (DDPS).	d) Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	**IA_{IN}**	Yes	Yes	Yes
C.I.11 Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the risk management plan	a) Implementation of wording agreed by the competent authority	**IA_{IN}**	Yes	Yes	Yes

Description	Subcategory	Type	Scientific Recommendation Non-Biologicals	Scientific Recommendation Biologicals/ Immunologicals	Conditions to be met/ documentation to be provided
C.I.z Implementation of changes in the SPC not already covered elsewhere in the Classification Guideline for which no new quality, pre-clinical, clinical or pharmacovigilance data are provided			Yes	Yes	Yes
C.I.z Editorial changes to SPC/PL/Labelling if inclusion in an upcoming procedure is not possible			Yes	Yes	Yes
C.II.6 Changes to the labelling or the package leaflet which are not connected with the summary of product characteristics.	a) Administrative information concerning the holder's representative	**IA_{IN}**	Yes	Yes	Yes
C.II.6 Changes to the labelling or the package leaflet which are not connected with the summary of product characteristics.	b) Other changes	**IB**	Yes	Yes	Yes
C.II.6 Changes to the labelling or the package leaflet which are not connected with the summary of product characteristics.	z) (11.12.2009) Inclusion of traceability stickers in product carton	**IA**	Yes	Yes	Yes
D.1 Change in the name and/or address of the Vaccine Antigen Master File (VAMF)certificate holder		**IA_{IN}**	n.a.	Yes	Yes
Art 5 recommendation-like process: Defined as not requiring assessment			Yes	Yes	Yes