Annex 7
(Art. 22a)

List of variations in accordance with Articles 21–24 TPO
as at 1 January 2019

Contents

1 List

Marketing authorisation holders of human and veterinary medicinal products must report the following changes in writing, or submit them for approval, to Swissmedic:

- A. Regulatory changes of types IA, IA_{IN} and IB
- B. Changes in quality of types IA, IA_{IN}, IB and II
- C. Safety, efficacy and pharmacovigilance changes of types IA_{IN}, IB and II
- X. Changes to PMF of types IA, IA_{IN}, IB and II
- Y. Various changes relating to complementary and herbal medicines of type IB
- Z. Extensions

This list corresponds to Annex 7 of the TPLRO and is the binding Ordinance text for Swissmedic and applicants.

Annex 7
(Art. 22a)

1.1 A. Regulatory changes

A.1 Change in the name and/or address of the marketing authorisation holder[1]	Conditions to be fulfilled	Documentation to be submitted	Type
	1, 2	1, 2, 3	IA_{IN}
Conditions			
1. The marketing authorisation holder must be the same legal person.			
2. A.1 is implemented after approval has been given for the change in the name/address of the establishment licence that is submitted at the same time.			
Documentation			
1. Not applicable to Switzerland.			
2. Not applicable to Switzerland.			
3. Basic form Application for an establishment licence – Medicinal products (I-301.AA.05-A02, particularly completed point 1) and Additional sheet F, Application for an establishment licence – Medicinal products (I-301.AA.05-A04).			

A.2 b) Change in the name of the medicinal product	Conditions to be fulfilled	Documentation to be submitted	Type
		2	IB
Documentation			
1. Not applicable to Switzerland.			
2. Revised product information and/or packaging texts.			

A.3 Change in the name of the active substance or of an excipient	Conditions to be fulfilled	Documentation to be submitted	Type
	1, 2	1, 2, 3	IA_{IN}
Conditions			
1. The active substance/excipient must remain the same.			
2. Not applicable to Switzerland.			
Documentation			
1. Proof of inclusion in the WHO ATC/DDD Index or copy of the INN List; if applicable, proof of conformity of the change with the pharmacopoeia; for herbal medicinal products, a declaration to the effect that the name is in accordance with the EMA Note for Guidance on Quality of (traditional) Herbal Medicinal Products and with the EMA Guideline on declaration of herbal substances and herbal preparations in (traditional) herbal medicinal products.			
2. Revised product information and/or packaging texts.			
3. *Full declaration HMV4* form with correspondingly changed names.			

A.4 Change in the name and/or address of a DMF holder, manufacturing site (if applicable also of the quality control testing sites) of the active substance or any starting material / reagent / intermediate used in the manufacture of the active substance, where the approved documentation does not include a Ph. Eur. Certificate of	Conditions to be fulfilled	Documentation to be submitted	Type

[1] This change **cannot** be part of a multiple application. An application to change the establishment licence as a result of a change in the name/address of the establishment licence holder causes Swissmedic to trigger A.1 (see also the guidance document *Change to name or address of marketing authorisation holder*).

Suitability (CEP), or in those of the manufacturer of a novel excipient (where specified in the dossier)			
	1	**1, 2, 3**	**IA**
Conditions			
1. The manufacturing site and all manufacturing operations must remain the same.			
Documentation			
1. An official document showing the new name and/or the new address.			
2. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products), including the updated *Manufacturer information HMV4* form, if applicable.			
3. In case of change in the name of the DMF holder, an updated Letter of Access.			

A.5 Change in the name and/or address of a manufacturer of the finished product (including batch release and quality control sites)	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) The activities for which the manufacturer is responsible also include batch releases.	**1**	**1, 2**	**IA_{IN}**
b) Batch releases are not included in the activities for which the manufacturer is responsible.	**1**	**1, 2**	**IA**
Conditions			
1. The manufacturing location and all manufacturing steps remain unchanged.			
Documentation			
1. A copy of the revised establishment licence (if one exists) or an official document showing the new name and/or the new address.			
2. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products), including the updated *Manufacturer information* HMV4 form and, if applicable, revised product information and/or packaging texts.			

A.6 Change in ATC code/ATCvet code	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
	1	**1, 2**	**IA**
Conditions			
1. Change following granting or amendment to the ATC/ATCvet code by the WHO.			
Documentation			
1. Proof of inclusion in the ATC/DDD Index and ATCvet Index respectively, or copy of the ATC/ATCvet code list.			
2. Revised product information and/or packaging texts.			

A.7 Deletion of sites for the manufacture of an active substance, intermediate or finished products, for packaging, for quality control, for batch release or of sites of suppliers/manufacturers of a starting material, reagent or excipient (provided these are listed in the dossier Module 3 / Part II)	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
	1, 2	**1, 2**	**IA**

Conditions
1. At least one previously authorised site performing the same functions as the site affected by the deletion should remain.
2. The deletion is not attributable to critical deficiencies concerning manufacturing.
Documentation
1. Comparison of present and proposed sites.
2. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products), including the updated *Manufacturer information HMV4* form, if applicable.

A.8 Change to date of the audit to verify GMP compliance of the active substance manufacturer	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
		1	**IA**
Documentation			
1. Written confirmation from the manufacturer of the finished product stating verification of compliance of the manufacturer of the active substance with the principles and guidelines of good manufacturing practices.			

A.100 Change in the product information and/or packaging texts without the submission of scientific data	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
		1	**IB**
Documentation			
1. Revised product information and/or packaging texts.			

A.101 Adaptation of a co-marketing medicinal product to ensure alignment with the basic product (for example in the event of changes in the product information and/or packaging texts or quality)	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) With variation of the packaging code.	**1, 2, 3, 4**	**1, 2, 3**	**IB**
b) Without variation of the packaging code.	**1, 2, 4**	**1, 2, 3**	**IA_{IN}**
Conditions			
1. The modified / new text passages for the basic product must be taken over unchanged.			
2. The product information texts (information for healthcare professionals and/or patient information) and their translations required by therapeutic products legislation must be uploaded to the Swissmedic publication platform and released (exception: export licence).			
3. Change in the basic product resulted in a change to the packaging code.			
4. Based on the duty of the authorisation holder of the basic product to notify changes that need to be taken over to the authorisation holder of the co-marketing medicinal product, the latter submits the respective change within 30 days of approval being granted for the basic product.			
Documentation			
1. In the case of changes to the product information, the most recently approved version of the information for healthcare professionals and/or patient information for the basic product, with corrections for the name of the medicinal product, authorisation number and marketing authorisation holder, should be submitted.			
2. If appropriate, relevant updated forms (e.g. *Full declaration HMV4* form, *Manufacturer information HMV4* form).			

3. In the case of quality changes and regulatory changes, the copy of the Swissmedic approval letter for the basic product should be submitted. For variations requiring notification (types IA, IA_{IN} and IB) that concern the basic product, a copy of the Swissmedic receipt of confirmation or a print-out of the relevant Swissmedic Portal entry should be submitted instead of the copy of the approval letter.

A.102 New and/or modified pack size	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
	1, 2, 3, 4, 5	**1, 2**	**IB**
Conditions			
1. No scientific data are submitted.			
2. Declaration that the new pack size is appropriate and consistent with the approved dosage regimen and duration of treatment stated in the information for healthcare professionals.			
3. If the additional pack size is a free sample pack, a "Free sample" label in at least two official languages must be clearly visible and permanently affixed to the pack.			
4. Sample packs must also be manufactured according to the rules of Good Manufacturing Practice (GMP).			
5. Sample packs of non-prescription medicinal products may contain a maximum of one daily dosage.			
Documentation			
1. Revised product information and/or packaging texts.			
2. If applicable, information on the primary packaging material used for sample packs if this is not identical to that described for the authorised product (material is described in Ph. Eur. Chapter 3.1, is allowed for foodstuffs, satisfies the general requirements of Ph. Eur. for containers (Chapters 1.3 and 3.2), brief description of the composition, etc.).			

A.103 Omission of a pack size	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
	1	**1**	**IA**
Conditions			
1. The dosage strength must be retained, and the dosage recommendation must continue to be valid for implementation.			
Documentation			
1. Revised product information and/or packaging texts.			

A.104 Conversion of a main authorisation to an export licence	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
	1	**1**	**IB**
Conditions			
1. It must not be an essential medicinal product.			
Documentation			
1. Revised product information (new: basic information).			

A.105 Conversion of an export licence to a main authorisation	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
		1	**IB**
Documentation			

1. Revised product information and/or packaging texts.

A.106 Conversion of the authorisation of a co-marketing medicinal product to independent authorisation (basic product)	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
	1	**1**	**IB**
Conditions			
1. No scientific data are submitted.			
Documentation			
1. Submission of a complete identical set of documentation. If the existing basic medicinal product dispenses with authorisation, its documentation can also be transcribed to the existing co-marketing medicinal product.			

A.107 Conversion of the authorisation from an independent authorisation (basic product) to co-marketing medicinal product	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
	1, 2	**1**	**IB**
Conditions			
1. No scientific data are submitted.			
2. A basic product must be authorised.			
Documentation			
1. Module 1, as for new submission for a co-marketing medicinal product.			

A.108 Change to an antivenin	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
	1	**1**	**IB**
Conditions			
1. The variation concerns an entry made on the latest *New authorisation variation of antivenom HMV4* form or on a document submitted additionally (e.g. changed foreign product information).			
Documentation			
1. Updated *New authorisation variation of antivenom HMV4* form.			

A.109 Implementation of new requirements in accordance with the revised TPLRO (as of 1.1.2019) ***Human medicinal products:*** Revision of the product information / packaging texts, including full declaration, warnings according to Annex 3a TPLRO ***Veterinary medicinal products:*** Revision of the veterinary product information / packaging texts to EU format, including full declaration in accordance with Annex 6 TPLRO	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
		1, 2, 3	**II**
Documentation			
1. Revised product information and/or packaging texts.			
2. Form *Full declaration HMV4*.			
3. For veterinary medicinal products: Documentation of statements proposed in addition to the product information approved by Swissmedic.			

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1.2 B. Quality changes

1.2.1 B.I. Active substance

B.I.a) Manufacture

B.I.a.1 Change in the manufacturer of a starting material / reagent / intermediate used in the manufacturing process of the active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	Conditions to be fulfilled	Documentation to be submitted	Type
a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	1, 2, 3	1, 2, 3, 4, 5, 6, 7	IA_{IN}
b) Introduction of a manufacturer of the active substance supported by a DMF			II
c) The proposed manufacturer uses a substantially different route of synthesis or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability			II
d) New manufacturer of material for which an assessment is required of viral safety and/or TSE risk			II
e) The change relates to a biological active substance or a starting material / reagent / intermediate used in the manufacture of a biological / immunological finished product			II
f) Changes to the quality control site for the active substance - replacement or addition of a site where batch control / testing takes place	2, 4	1, 5	IA
g) Introduction of a new manufacturer of the active substance that is not supported by a DMF and that requires significant update to the relevant active substance section of the dossier			II
h) Addition of an alternative sterilisation site for the active substance using a Ph. Eur. method		1, 2, 4, 5, 8	IB
i) Introduction of a new site of micronisation	2, 5	1, 4, 5, 6	IA
j) Changes to the quality control site for a biological active substance: replacement or addition of a site where batch control / testing including a biological / immunological / immunochemical method takes place			II
k) New storage site of Master Cell Bank and/or Working Cell Bank		1, 5	IB
Conditions			

1. For starting materials and reagents, the specifications (including in process controls, methods of analysis ofall materials), are identical to those already approved. For intermediates and active substances, the specifications (including in process controls, methods of analysis of all materials), method of preparation (including batch size) and detailed route of synthesis are identical to those already approved.
2. The active substance is neither a biological/immunological substance nor sterile.
3. Where materials of human or animal origin are used in the manufacturing process, the manufacturer does not use any new supplier for which assessment is required of viral safety or of compliance with the current "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products".
4. Method transfer from the old to the new site has been successfully completed.
5. The particle size specification of the active substance and the corresponding analytical method remain the same.
Documentation
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products), including the updated *Manufacturer information HMV4* form, if applicable.
2. A declaration from the marketing authorisation holder or DMF Holder stating that the synthetic route (or in the case of herbal medicinal products, where appropriate the manufacturing method and the processing of herbal drug), quality control procedures and specifications of the active substance and of the starting material / reagent / intermediate used in the manufacturing process of the active substance are the same as those already approved.
3. Either a TSE Ph. Eur. Certificate of Suitability for any new source of material or, where applicable, documentary evidence that the specific source of the TSE risk material complies with the current "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" and an updated *Substances of Animal and Human Origin HMV4* form.
4. Batch analysis data (in the form of a comparative table) for at least two batches (minimum pilot scale) of the active substance from the current and proposed manufacturers / sites.
5. Comparison of present and proposed manufacturers.
6. Completed and signed form *Declaration by the Responsible Person for foreign manufacturers HMV4*, if applicable.
7. If applicable, a commitment by the active substance manufacturer to inform the marketing authorisation holder of any changes to the manufacturing process, specifications or test procedures of the active substance.
8. Proof that the site's GMP compliance has been verified.

B.I.a.2 Changes in the manufacturing process of the active substance	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Minor change in the manufacturing process of the active substance	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 3**	**IA**
b) Substantial change to the manufacturing process of the active substance which may have a significant impact on the quality, safety or efficacy of the finished product.			**II**
c) The change relates to a biological/immunological substance or the use of a different chemically derived substance in the manufacture of a biological/immunological substance, which may have a significant			**II**

impact on the quality, safety and efficacy of the finished product and is not related to a protocol			
d) The change relates to a herbal medicinal product and there is a change to one of the following: manufacturing route or production			**II**
e) Minor change to the restricted part of the DMF		**1, 2, 3, 4**	**IB**
Conditions			
1. No adverse change in the qualitative or quantitative impurity profile or in physico-chemical properties.			
2. The synthetic route remains the same, i.e. intermediates remain the same, and no new reagents, catalysts or solvents are used in the process. In the case of herbal medicinal products, the production of the herbal substance and the manufacturing route remain the same.			
3. The specifications of the active substance or intermediates remain the same.			
4. The change is fully described in the applicant's part of the DMF, if applicable.			
5. The active substance is not a biological/immunological substance.			
6. The change does not relate to the manufacturing route or the production of a herbal medicinal product.			
7. The change does not relate to a restricted part of the DMF.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products, as appropriate) and of the approved DMF, if applicable, including a comparison of the present process and the proposed process.			
2. Batch analysis data (in the form of a comparative table) for at least two batches (minimum pilot scale) of the active substance that were manufactured according to the currently approved and proposed manufacturing processes.			
3. A copy of the approved specifications of the active substance.			
4. A declaration from the marketing authorisation holder or the DMF holder stating that there is no change in qualitative and quantitative impurity profile or in physico-chemical properties, that the synthetic route remains the same and that the specifications of the active substance or intermediates are unchanged.			
Note on B.I.a.2.b: For chemical active substances, this refers to substantial changes to the synthetic route or manufacturing conditions which may have a potential to change important quality characteristics of the active substance, such as the qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability.			

B.I.a.3 Change in batch size (incl. batch size range) of the active substance or any intermediate used in the manufacture of an active substance	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Up to 10-fold increase compared to the originally approved batch size	**1, 2, 3, 4, 6, 7, 8**	**1, 2, 5**	**IA**
b) Downscaling down to 10-fold	**1, 2, 3, 4, 5**	**1, 2, 5**	**IA**
c) The change requires assessment of the comparability of a biological / immunological active substance			**II**
d) More than 10-fold increase compared to the originally approved batch size		**1, 2, 3, 4**	**IB**
e) The scale for a biological / immunological active substance is increased or decreased		**1, 2, 3, 4**	**IB**

without any change in the manufacturing process (e.g. duplication of the production lines)			
Conditions			
1. Any changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment.			
2. Test results of at least two batches according to the specifications should be available for the proposed batch size			
3. The product is not a biological / immunological medicinal product.			
4. The change does not adversely affect the reproducibility of the process.			
5. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
6. The specifications of the active substance / intermediates remain unchanged.			
7. The active substance is not sterile.			
8. The batch size is within the 10-fold range of the batch size foreseen when the marketing authorisation was granted, or following a subsequent change not agreed as a Type IA variation.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products).			
2. The batch numbers of the tested batches having the proposed batch size.			
3. Batch analysis data (in the form of a comparative table) for a minimum of one production batch of the active substance or intermediate as appropriate, manufactured to both the currently approved and the proposed sizes. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).			
4. A copy of the approved specifications of the active substance or intermediate.			
5. A declaration from the marketing authorisation holder or the DMF holder stating that the changes to the manufacturing methods are only those necessitated by scale-up or downscaling, e.g. use of different-sized equipment, that the change does not adversely affect the reproducibility of the process, that it is not the result of unexpected events arising during manufacture or because of stability concerns, and that the specifications of the active substance / intermediates remain the same.			

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

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity or change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes to the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).
7. The specification parameter does not concern a critical parameter, e.g. assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water content, any request for changing the frequency of testing.
Documentation
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products).
2. Comparison of current and proposed in-process tests.
3. Details of any new non-pharmacopoeial analytical method and validation data, where relevant.
4. Batch analysis data for two production batches (three production batches for biologicals, unless otherwise justified) of the active substance for all specification parameters.
5. Justification/risk assessment from the marketing authorisation holder or the DMF holder showing that the in-process tests are non-significant, or that the in-process tests are obsolete.
6. Justification from the MAH or DMF holder for the new in-process tests and limits.

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

B.I.b) Control of active substance

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material / intermediate / reagent used in the manufacturing process of the active substance	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release	**1, 2, 3, 4**	**1, 2**	**IA_{IN}**
b) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
c) Addition of a new specification parameter with its corresponding test method	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 7**	**IA**
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**1, 2, 8**	**1, 2, 6**	**IA**

e) Deletion of a specification parameter which may have a significant effect on the overall quality of the active substance and/or the finished product			**II**
f) Change outside the approved specifications limits range for the active substance			**II**
g) Widening of the approved specifications limits for starting materials / intermediates, which may have a significant effect on the overall quality of the active substance and/or the finished product			**II**
h) Addition or replacement (excluding biological or immunological substances) of a specification parameter with its corresponding test method as a result of a safety or quality issue		**1, 2, 3, 4, 5, 7**	**IB**
i) Where there is no monograph in the European Pharmacopoeia or the Pharmacopoeia Helvetica for an active substance, a change in specification from in-house to a non-official pharmacopoeia or a pharmacopoeia of a third country		**1, 2, 3, 4, 5, 7**	**IB**

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity or change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes to the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).
7. For any material, the change does not concern a genotoxic impurity. If the change involves the final active substance, other than for residual solvents which must be in line with ICH/VICH limits, the specifications for new impurities should be in line with Ph. Eur. or Pharmacopoeia Helvetica.
8. The specification parameter does not concern a critical parameter, e.g. assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics, e.g. particle size, bulk or tapped density, identity test, water content, any request for skip testing.

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products).
2. Comparison of current and proposed specifications.
3. Details of the new analytical method and validation data, where relevant.
4. Batch analysis data for two production batches (three production batches for biologicals, unless otherwise justified) of the relevant substance for all specification parameters.

5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specifications. For herbal medicinal products, comparative disintegration data may be acceptable.
6. Justification/risk assessment from the marketing authorisation holder or the DMF holder showing that the parameter is non-significant, or that it is obsolete.
7. Justification from the marketing authorisation holder or DMF holder for the new specification parameter and the limits.

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

Conditions
1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the previously approved test procedure.
2. No changes have been made to the total impurity limits, and no new unqualified impurities have been detected.
3. The analytical method essentially remains the same (e.g. a change in column length or temperature, but not a different type of column or method).
4. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The active substance is not a biological/immunological substance.
7. An alternative test procedure is already authorised for the specification parameter, and this procedure has not been added through IA/IAIN notification.
Documentation
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products), including a description of the analytical method, a summary of the validation data and, if applicable, revised specifications for impurities.

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

B.I.c) Container closure system

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

Conditions
1. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.
2. Relevant stability studies have been started under ICH/VICH conditions, 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 the time of implementation. However, if the proposed packaging is more resistant than the existing packaging, the three months' stability data do not yet have to be available. These studies must be finalised, and the data will be provided immediately to Swissmedic if outside specifications or potentially outside specifications at the end of the shelf-life/retest period (with proposed action).
3. Sterile, liquid and biological / immunological active substances are excluded.
Documentation
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products).
2. Appropriate data on the new packaging (e.g. comparative data on permeability e.g. for O2, CO2 moisture), including a confirmation that the material complies with relevant pharmacopoeial requirements or legislation on materials and articles intended to come into contact with food (requirements of the "Ordinance of the FDHA on materials and articles intended to come into contact with foodstuffs" (Consumer Goods Ordinance; SR 817.023.21)).
3. Where appropriate, proof must be provided that no interaction between the content and the packaging material occurs (e.g. no migration of components of the proposed material into the content and no loss of components of the product into the pack), including confirmation that the material complies with relevant pharmacopoeia requirements or legislation on materials and articles intended to come into contact with food (requirements of the "Ordinance of the FDHA on materials and articles intended to come into contact with foodstuffs" (Consumer Goods Ordinance; SR 817.023.21)).
4. A declaration from the marketing authorisation holder or the DMF holder stating 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 the time of implementation and that the available data did not indicate a problem. It should also be confirmed that the studies will be finalised and that data will be provided immediately to Swissmedic 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 three months, and confirmation that these studies will be finalised, and that data will be provided immediately to Swissmedic if outside specifications, or potentially outside specifications, at the end of the approved retest period (with proposed action).

6. If applicable, comparison of the current and proposed immediate packaging specifications.

B.I.c.2 Change in the specification parameters and/or limits of the immediate packaging of the active substance	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter with its corresponding test method	**1, 2, 5**	**1, 2, 3, 4, 6**	**IA**
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**1, 2**	**1, 2, 5**	**IA**
d) Addition or replacement of a specification parameter as a result of a safety or quality issue		**1, 2, 3, 4, 6**	**IB**
Conditions			
1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure) unless it has been previously assessed and agreed as part of a follow-up measure.			
2. The change does not result from unexpected events arising during manufacture of the packaging material or during storage of the active substance.			
3. Any change should be within the range of currently approved limits.			
4. The test procedure remains the same, or changes to 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 CTD format or NTA format for veterinary medicinal products).			
2. Comparison of current and proposed specifications.			
3. Details of the new analytical method and validation data, where relevant.			
4. Batch analysis data on two batches of the immediate packaging for all specification parameters.			
5. Justification/risk assessment from the marketing authorisation holder or the DMF holder showing that the parameter is non-significant, or that it is obsolete.			
6. Justification from the marketing authorisation holder or DMF holder for the new specification parameter and the limits.			

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

2. The analytical method essentially remains 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 a biological / immunological substance.
5. There is still a test procedure registered for the specification parameter, and this procedure has not been added through IA/IAIN notification.
Documentation
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary products), including a description of the analytical method and a summary of the validation data.
2. Comparative validation results or, if justified, comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.

B.I.d) Stability

B.I.d.1 Change in the retest period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability (CEP) covering the retest period is part of the approved dossier	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Retest period / storage period			
1. Reduction	**1**	**1, 2, 3**	**IA**
2. Extension of the retest period based on extrapolation of stability data not in accordance with ICH/VICH guidelines (not applicable for biological / immunological active substances)			**II**
3. Extension of storage period of a biological / immunological active substance not in accordance with an approved stability protocol			**II**
4. Extension or introduction of a retest period / storage period supported by real time data		**1, 2, 3**	**IB**
b) Storage conditions			
1. Change to more restrictive storage conditions of the active substance	**1**	**1, 2, 3**	**IA**
2. Change in storage conditions of biological / immunological active substances, when the stability studies have not been performed in accordance with a currently approved stability protocol			**II**
3. Change in storage conditions of the active substance		**1, 2, 3**	**IB**
c) 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.			
2. The changes do 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
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products). This must contain results of appropriate real-time stability studies conducted in accordance with the relevant stability guidelines on at least two (three for biological medicinal products) pilot or production-scale batches of the active substance in the authorised packaging material and covering the duration of the requested retest period or requested storage conditions.
2. Confirmation that stability studies have been done to the currently approved protocol. The studies must show that the agreed relevant specifications are still met.
3. Copy of approved specifications of the active substance.
4. Justification for the proposed changes.

B.I.e) Design space and post approval change management protocol

B.I.e.1 Introduction of a new design space or extension of an approved design space for the active substance, concerning:	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) One unit operation in the manufacturing process of the active substance including the resulting in-process controls and/or test procedures		**1, 2, 3**	**II**
b) Test procedures for starting materials / reagents / intermediates and/or the active substance		**1, 2, 3**	**II**
Documentation			
1. The design space has been developed in accordance with the relevant international scientific guidelines. Results from product, process and analytical development studies (e.g. interaction of the different parameters forming the design space have to be studied, including risk assessment and multivariate studies, as appropriate) demonstrating where relevant that a systematic mechanistic understanding of material attributes and process parameters to the critical quality attributes of the active substance has been achieved.			
2. Description of the design space in tabular format, including the variables (material attributes and process parameters, as appropriate) and their proposed ranges.			
3. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products).			

B.I.e.2 Introduction of a post approval change management protocol related to the active substance	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
		1, 2, 3	**II**
Documentation			
1. Detailed description for the proposed change.			
2. Change management protocol related to the active substance.			
3. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products).			

B.I.e.3 Deletion of an approved change management protocol related to the active substance	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
	1	**1, 2**	**IA_{IN}**

Conditions
1. The deletion of the approved change management protocol related to the active substance is not due to unexpected events or to out-of-specification results during the implementation of the changes described in the protocol and does not have any effect on the already approved information in the dossier.
Documentation
1. Justification for the proposed deletion.
2. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products).

B.I.e.4 Changes to an approved change management protocol	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Major changes to an approved change management protocol			**II**
b) Minor changes to an approved 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.I.e.5 Implementation of changes foreseen in an approved change management protocol	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) The implementation of the change requires no further supportive data	**1**	**1, 2, 4**	**IA_{IN}**
b) The implementation of the change requires further supportive data		**1, 2, 3, 4**	**IB**
c) Implementation of a change for a biological/immunological medicinal product		**1, 2, 3, 4, 5**	**IB**
Conditions			
1. The proposed change has been performed fully in line with the approved change management protocol.			
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 CTD format or NTA format for veterinary medicinal products).			
5. Copy of approved specifications of the active substance.			

1.2.2 B.II. Finished product

B.II.a) Description and composition

B.II.a.1 Change or addition of imprints, bossing or other markings including replacement or addition of inks used for product marking.	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Changes in imprints, bossing or other markings	**1, 2, 3, 4, 5**	**1, 2**	**IA_{IN}**
b) Changes in scoring/break lines intended to divide into equal doses		**1, 2, 3**	**IB**
Conditions			
1. Finished product release and end of shelf-life specifications have not been changed (except for appearance)			
2. Any ink must comply with the relevant pharmaceutical legislation.			
3. The scoring/break lines are not intended to divide into equal doses.			
4. Any product markings used to differentiate dosage strengths should not be completely deleted.			
5. If the change also involves a co-marketing medicinal product, the change (e.g. imprint/bossing) must be compatible with the co-marketing medicinal product, see guidance document *Authorisation of co-marketing medicinal products HMV4*.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary products), including a detailed drawing or written description of the current and new appearance, and including revised product information and/or packaging texts as appropriate.			
2. Not applicable to Switzerland.			
3. Results of the appropriate Ph. Eur. tests demonstrating equivalence in characteristics / correct dosing.			

B.II.a.2 Change in the shape or dimensions of the pharmaceutical form	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Immediate-release tablets, capsules, suppositories and pessaries	**1, 2, 3, 4**	**1, 4**	**IA_{IN}**
b) Gastro-resistant, modified or prolonged-release pharmaceutical forms and scored tablets intended to be divided into equal doses		**1, 2, 3, 4, 5**	**IB**
c) Addition of a new kit for a radiopharmaceutical preparation with another fill volume			**II**
Conditions			
1. If appropriate, the dissolution profile of the reformulated product is comparable to the old one. For herbal medicinal products, where dissolution testing may not be feasible, the disintegration time of the new product compared to the old one.			
2. Release and end of shelf-life specifications of the finished product have not been changed (except for dimensions).			
3. The qualitative or quantitative composition and mean mass remain unchanged.			
4. The change does not relate to a scored tablet that is intended to be divided into equal doses.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary products), including a detailed drawing of the current and proposed situation, and including revised product information and/or packaging texts as appropriate.			

2. Comparative dissolution data on at least one pilot batch of the current and proposed dimensions (no significant differences regarding comparability see the relevant guidance on bioavailability (human or veterinary medicinal products). For herbal medicinal products, comparative disintegration data may be acceptable.
3. Justification for not submitting a new bioequivalence study according to the relevant guidance on bioavailability (human or veterinary medicinal products).
4. Not applicable to Switzerland.
5. Results of the appropriate Ph. Eur. tests demonstrating equivalence in characteristics / correct dosing.
Note on B.II.a.2.c: Applicants are reminded that any changes to the dosage strength of the medicinal product requires the submission of an extension application.

B.II.a.3 Changes in the composition (excipients) of the finished product	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Changes in components of the flavouring or colouring system			
1. Addition, deletion or replacement	**1, 2, 3, 4, 5, 6, 7, 9, 11**	**1, 2, 4, 5, 6**	**IA_{IN}**
2. Increase or reduction	**1, 2, 3, 4, 11**	**1, 2, 4**	**IA**
3. Biological veterinary medicinal products for oral use for which the colouring or flavouring agent is important for the uptake by target animal species			**II**
b) Other excipients			
1. Any minor adjustment of the quantitative composition of the finished product with respect to excipients	**1, 2, 4, 8, 9, 10**	**1, 2, 7**	**IA**
2. Qualitative or quantitative changes in one or more excipients that may have a significant impact on the safety, quality or efficacy of the finished product			**II**
3. Change that relates to a biological / immunological product			**II**
4. Any new excipient that includes the use of materials of human or animal origin for which assessment is required of viral safety data or TSE risk			**II**
5. Change that is supported by a bioequivalence study			**II**
6. Replacement of a single excipient with a comparable excipient with the same functional characteristics and at a similar level		**1, 3, 4, 5, 6, 7, 8, 9, 10**	**IB**
Conditions			
1. No change in functional characteristics of the pharmaceutical form, e.g. disintegration time, dissolution profile.			
2. Any minor adjustment to the formulation to maintain the total weight should be made by an excipient which currently makes up a major part of the finished product formulation.			

3. The finished product specification has only been updated in respect of appearance / odour / taste and if relevant, deletion of an identification test.
4. Stability studies have been started under ICH/VICH conditions (with indication of batch numbers) and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant (at time of implementation for type IA and at time of notification for type IB variations) and that the stability profile is similar to the currently registered situation. It should be confirmed that these studies will be finalised and that data will be provided immediately to Swissmedic if outside specifications or potentially outside specification at the end of the approved shelf-life (with proposed action). In addition, where relevant, photostability testing should be performed.
5. Any new proposed components must comply with the relevant food legislation (e.g. "Ordinance of the FDHA on Additives permitted in Foodstuffs" [Food Additives Ordinance; FoodAO; SR 817.022.31], "Ordinance of the FDHA on Flavourings and Food Ingredients with Flavouring Properties" [Flavourings Ordinance; SR 817.022.41]).
6. Any new component does not include the use of materials of human or animal origin for which assessment is required of viral safety data or compliance with the current "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products".
7. Where applicable, the change does not affect the differentiation between dosage strengths and does not have a negative impact on taste acceptability for paediatric formulations.
8. The dissolution profile of the new finished product determined on a minimum of two pilot scale batches is comparable to the old one (no significant differences regarding comparability, see the relevant guidance on bioavailability (human or veterinary medicinal products)). For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.
9. The change is not the result of stability issues and/or should not result in potential safety concerns i.e. differentiation between dosage strengths.
10. The product is not a biological / immunological medicinal product.
11. For veterinary medicinal products for oral use, the change does not affect the uptake by target animal species.
Documentation
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary products, as appropriate), including identification method for any new colouring agent, where relevant, and including revised product information and packaging texts and *Full declaration HMV4* form as appropriate.
2. A declaration stating 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 the time of implementation and that the available data did not indicate a problem. It should also be confirmed that the studies will be finalised and that data will be provided immediately to Swissmedic if outside specifications, or potentially outside specifications, at the end of the approved shelf-life (with proposed action).
3. The results of stability studies that have been carried out under ICH/VICH conditions, on the relevant stability parameters, on at least two pilot or industrial scale batches, covering a minimum period of three months, and confirmation that these studies will be finalised, and that data will be provided immediately to Swissmedic if outside specifications, or potentially outside specifications, at the end of the approved shelf-life (with proposed action).
4. Not applicable to Switzerland.
5. Either a TSE Ph. Eur. Certificate of Suitability for any new source of material derived from animals susceptible to TSE risk or, where applicable, documentary evidence that the specific

source of the TSE risk material (including substances used in the manufacture of the active substance/excipient) complies with the current "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products". The following information should be included for each such material: Name of manufacturer, species and tissues from which the material is a derivative, country of origin of the source animals and its use. In addition, an updated *Substances of animal or human origin HMV4* form.
6. Data to demonstrate that the new excipient does not interfere with the finished product specification test methods, if appropriate.
7. Justification for the change/choice of excipients etc. must be given by appropriate pharmaceutical development (including stability aspects and antimicrobial preservation where appropriate).
8. For solid pharmaceutical forms, comparative dissolution profile data on at least two pilot scale batches of the finished product in the new and old composition. For herbal medicinal products, comparative disintegration data may be acceptable.
9. Justification for not submitting a new bioequivalence study according to the current guidance on bioequivalence.
10. For veterinary medicines intended for use in food-producing animal species, proof that any excipient residues in animal tissue is non-hazardous according to the state-of-the-art in science and technology or, if not, justification that the excipient does not have pharmacological activity at the dose at which it is administered to the target animal.

B.II.a.4 Change in coating weight of oral pharmaceutical forms or change in weight of capsule shells	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Solid oral pharmaceutical forms	**1, 2, 3, 4**	**1, 2**	**IA**
b) Gastro-resistant, modified- or prolonged-release pharmaceutical forms where the coating is a critical factor for the release mechanism			**II**
Conditions			
1. The dissolution profile of the new product determined on a minimum of two pilot scale batches is comparable to the old one. For herbal medicinal products where dissolution testing may not be feasible, the disintegration time of the new product is comparable to the old one.			
2. The coating is not a critical factor for the release mechanism.			
3. The finished product specification has only been updated in respect of weight and dimensions, if applicable.			
4. Stability studies in accordance with ICH/VICH conditions have been started with at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant at the time of implementation and confirmation that these studies will be finalised. Data will be provided immediately to Swissmedic 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 CTD format or NTA format for veterinary medicinal products).			
2. A declaration stating 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 the time of implementation and that the available data did not indicate a problem. It should also be confirmed that the studies will be finalised and that data will be provided immediately to			

Swissmedic if outside specifications, or potentially outside specifications, at the end of the approved shelf-life (with proposed action). In addition, where relevant, photostability testing should be performed.

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

B.II.a.6 Deletion of the solvent / diluent container from the pack	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
		1, 2	**IB**
Documentation			
1. Justification for the deletion, including a statement regarding alternative means to obtain the solvent / diluent as required for the safe and effective use of the medicinal product.			
2. Revised product information and/or packaging texts.			

B.II.b) Manufacture

B.II.b.1 Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Secondary packaging site	**1, 2**	**1, 3, 8**	**IA_{IN}**
b) Primary packaging site	**1, 2, 3, 4, 5**	**1, 2, 3, 4, 8, 9**	**IA_{IN}**
c) Site where any manufacturing operations take place, except batch release, batch control (quality control), and secondary packaging, for biological / immunological medicinal products, or for pharmaceutical forms manufactured by complex manufacturing processes			**II**
d) Site which requires an initial or product-specific inspection			**II**
e) Site where any manufacturing operations take place, except batch-release, batch control (quality control), primary and secondary packaging, for non-sterile medicinal products		**1, 2, 3, 4, 5, 6, 7, 8, 9**	**IB**
f) Site where any manufacturing operations take place, except batch release, batch control (quality control), and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological / immunological medicinal products		**1, 2, 3, 4, 5, 6, 7, 8**	**IB**
Conditions			
1. The site is GMP compliant.			
2. Site appropriately authorised (to manufacture the pharmaceutical form or product concerned).			
3. The product is not a sterile product.			
4. Where relevant, for instance for suspensions and emulsions, validation scheme is available, or validation of the manufacture at the new site has been successfully carried out according to the current protocol with at least three production scale batches.			

5. The product is not a biological / immunological medicinal product.
Documentation
1. Proof that the manufacturer's GMP compliance has been verified.
2. Where relevant, the batch numbers, corresponding batch size and the manufacturing date of batches (≥3) used in the validation study should be indicated and the validation data presented, or validation protocol (scheme) submitted.
3. Comparison of present and proposed sites.
4. Copy of approved release and end-of-shelf-life specifications if relevant.
5. Batch analysis data on one production batch and two pilot-scale batches simulating the commercial production process (or two production batches) and comparative data on the last three batches from the previous site. Batch data on the next two production batches should be available on request or reported if outside specifications (with proposed action).
6. For semisolid and liquid formulations in which the active substance is present in non-dissolved form, appropriate validation data, including microscopic imaging of particle size distribution and morphology or any other appropriate imaging technique.
7. Completed and signed form *Declaration by the Responsible Person for foreign manufacturers HMV4*.
8. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products), including the updated *Manufacturer information HMV4* form.
9. If the manufacturing site and the primary packaging site are different, conditions of transport and bulk storage should be specified and validated.
Note: The guidance document *GMP compliance by foreign manufacturers HMV4* should be consulted for the GMP requirements for foreign manufacturers.

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

3. The product is not a biological / immunological medicinal product.
4. Method transfer from the old to the new site or new test laboratory has been successfully completed.
5. At least one batch release and quality control site remains in the dossier.
Documentation
1. Proof that the manufacturer's or testing laboratory's GMP compliance has been verified.
2. Comparison of present and proposed sites.
3. Not applicable to Switzerland.
4. Not applicable to Switzerland.
5. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products), including the updated *Manufacturer information HMV4* form and, if applicable, revised product information and/or packaging texts.

B.II.b.3 Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Minor change in the manufacturing process	**1, 2, 3, 4, 5, 6, 7**	**1, 2, 3, 4, 5, 6, 7, 8**	**IA**
b) Substantial changes to the manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product			**II**
c) The product is a biological / immunological finished product and the change requires an assessment of comparability			**II**
d) Introduction of a non-standard terminal sterilisation method			**II**
e) Introduction or increase in the overage used for the active substance			**II**
f) Minor change in the manufacturing process of an aqueous oral suspension		**1, 2, 4, 6, 7, 8**	**IB**
Conditions			
1. No change in qualitative and quantitative impurity profile or in physico-chemical properties.			
2. Either the change relates to an immediate-release solid oral pharmaceutical form or oral solution, and the medicinal product concerned is not a biological / immunological or herbal medicinal product; or the change relates to process parameters that, in the context of a previous assessment, have been considered to have no impact on the quality of the finished product (regardless of the type of product and/or pharmaceutical form).			
3. The manufacturing principle including the single manufacturing steps remain the same (e.g. processing intermediates), and there are no changes to any manufacturing solvent used in the process.			
4. The currently registered process has to be controlled by relevant in-process controls, and no changes (widening or deletion of limits) are required for these in-process controls.			
5. The specifications of the finished product or intermediates are unchanged.			
6. The new process must lead to an identical product regarding all aspects of quality, safety and efficacy.			
7. Relevant stability studies in accordance with the ICH/VICH conditions have been started with at least one pilot scale or industrial scale batch and at least three months stability data are at the			

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

B.II.b.4 Change in the batch size (including batch size range) of the finished product	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Up to 10-fold increase compared to the originally approved batch size	**1, 2, 3, 4, 5, 7**	**1, 4**	**IA**
b) Downscaling down to 10-fold	**1, 2, 3, 4, 5, 6**	**1, 4**	**IA**
c) The change requires assessment of the comparability of a biological / immunological medicinal product, or the change in batch size requires a new bioequivalence study			**II**
d) The change relates to all other pharmaceutical forms manufactured by a complex manufacturing process			**II**
e) More than 10-fold increase compared to the originally approved batch size for immediate-release oral pharmaceutical forms		**1, 2, 3, 4, 5, 6**	**IB**

f) The scale for a biological / immunological medicinal product is increased or decreased without any change in the manufacturing process (e.g. duplication of the production lines)		**1, 2, 3, 4, 5, 6**	**IB**
Conditions			
1. The change does not affect the reproducibility and/or consistency of the product.			
2. The change relates to conventional immediate-release oral pharmaceutical forms or non-sterile liquid pharmaceutical forms.			
3. Any changes to the manufacturing methods and/or to the in-process controls are only those necessitated by the change in batch-size, e.g. use of different sized equipment of the same type.			
4. Validation scheme is available, or validation of the manufacture has been successfully carried out according to the current protocol with at least three batches at the proposed new batch size in accordance with the relevant guidelines.			
5. The product is not a biological / immunological medicinal product.			
6. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.			
7. The batch size is within the 10-fold range of the batch size foreseen when the marketing authorisation was granted, or following a subsequent change not agreed as a Type IA variation.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products).			
2. Batch analysis data (in a comparative tabulated format) for a minimum of one production batch manufactured in both the currently approved and the proposed batch sizes. Batch data on the next two full production batches should be made available upon request and reported by the marketing authorisation holder if outside specification (with proposed action).			
3. Copy of approved release and end-of-shelf-life specifications.			
4. Where relevant, the batch numbers, corresponding batch size and the manufacturing date of batches (≥3) used in the validation study should be indicated or the validation protocol (scheme) be submitted.			
5. The validation results should be provided.			
6. The results of stability studies that have been carried out under ICH/VICH conditions, on the relevant stability parameters, on at least one pilot or industrial scale batch, covering a minimum period of three months, and confirmation that these studies will be finalised, and that data will be provided immediately to Swissmedic if outside specifications, or potentially outside specifications, at the end of the approved shelf-life (with proposed action). For biological / immunological medicinal products: a declaration that an assessment of comparability is not required.			

B.II.b.5 Change to in-process tests or limits applied during the manufacture of the finished product	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Tightening of in-process limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of new in-process tests and limits	**1, 2, 5, 6**	**1, 2, 3, 4, 5, 7**	**IA**
c) Deletion of a non-significant in-process test	**1, 2, 7**	**1, 2, 6**	**IA**
d) Deletion of an in-process test which may have a significant effect on the overall quality of the finished product			**II**

e) Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the finished product			**II**
f) Addition or replacement of an in-process test as a result of a safety or quality issue		**1, 2, 3, 4, 5, 7**	**IB**
Conditions			
1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).			
2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity or change in total impurity limits.			
3. Any change should be within the range of currently approved limits.			
4. The test procedure remains the same, or changes to the test procedure are minor.			
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.			
6. The new test method is not a biological/immunological/immunochemical method or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).			
7. The in-process test does not concern the control of a critical parameter, e.g. assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics (particle size, bulk or tapped density...), identity test (unless there is a suitable alternative control already present), microbiological control (unless not required for the particular pharmaceutical form).			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products).			
2. Comparison of current and proposed in-process tests and limits.			
3. Details of any new analytical method and validation data, where relevant.			
4. Batch analysis data for two production batches (three production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters.			
5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch manufactured using the current and new in-process tests. For herbal medicinal products, comparative disintegration data may be acceptable.			
6. Justification/risk assessment showing that the in-process test is non-significant or that it is obsolete.			
7. Justification of the new in-process tests and limits.			

Annex 7
(Art. 22a)

B.II.c) Control of excipients

B.II.c.1 Change in the specification parameters and/or limits of an excipient	Conditions to be fulfilled	Documentation to be submitted	Type
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter with its corresponding test method	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 6, 8**	**IA**
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	**1, 2, 8**	**1, 2, 7**	**IA**
d) Change outside the approved specifications limits range			**II**
e) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product			**II**
f) Addition or replacement (excluding biological or immunological products) of a specification parameter with its corresponding test method, as a result of a safety or quality issue		**1, 2, 3, 4, 5, 6, 8**	**IB**
g) Where there is no monograph in the European Pharmacopoeia or the Pharmacopoeia Helvetica for the excipient, a change in specification from in-house to a non-official pharmacopoeia or a pharmacopoeia of a third country		**1, 2, 3, 4, 5, 6, 8**	**IB**

Conditions

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture e.g. new unqualified impurity or change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes to the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The test method is not a biological / immunological / immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).
7. The change does not concern a genotoxic impurity.
8. The specification parameter does not concern the control of a critical parameter, e.g. impurities (unless a particular solvent is definitely not used in the manufacture of the excipient), any critical physical characteristics (particle size, bulk or tapped density...), identity test (unless there is a suitable alternative control already present), microbiological control (unless not required for the particular pharmaceutical form).

Documentation

1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products).
2. Comparison of current and proposed specifications.
3. Details of any new analytical method and validation data, where relevant.
4. Batch analysis data for two production batches (three production batches for biological excipients) of the excipient for all specification parameters.

5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch containing the excipient complying with the current and proposed specifications. For herbal medicinal products, comparative disintegration data may be acceptable.
6. If appropriate, justification for not submitting a new bioequivalence study according to the relevant guidance on bioavailability (human or veterinary medicinal products).
7. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.
8. Justification of the new specification parameter and the limits.

B.II.c.2 Change in test procedures for an excipient	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Minor changes to an approved test procedure	**1, 2, 3, 4**	**1, 2**	**IA**
b) Deletion of a test procedure if an alternative test procedure is already authorised	**5**	**1**	**IA**
c) Substantial change to, or replacement of, a biological / immunological / immunochemical test method or a method using a biological reagent			**II**
d) Other changes to a test procedure (including replacement or addition)		**1, 2**	**IB**
Conditions			
1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the previously approved test procedure.			
2. No changes have been made to the total impurity limits, and no new unqualified impurities have been detected.			
3. The analytical method essentially remains the same (e.g. a change in column length or temperature, but not a different type of column or method).			
4. The test method is not a biological / immunological / immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).			
5. An alternative test procedure is already authorised for the specification parameter, and this procedure has not been added through IA/IAIN notification.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary products), including a description of the analytical method, a summary of the validation data and, if applicable, revised specifications for impurities.			
2. Comparative validation results or, if justified, comparative analysis results showing that the current test and the proposed one are equivalent. This requirement is not applicable in case of an addition of a new test procedure.			

B.II.c.3 Change in source of an excipient or reagent with TSE risk	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) From TSE risk material to material of vegetable or synthetic origin			
1. For excipients or reagents not used in the manufacture of a biological / immunological active substance or in a biological / immunological medicinal product	**1**	**1**	**IA**
2. For excipients or reagents used in the manufacture of a biological / immunological		**1, 2**	**IB**

active substance or in a biological / immunological medicinal product			
b) Change or introduction of a TSE risk material, or replacement of a TSE risk material from a different TSE risk material, not covered by a TSE certificate of suitability			**II**
Conditions			
1. Excipient and finished product release and end of shelf-life specifications remain the same.			
Documentation			
1. Declaration from the manufacturer or the marketing authorisation holder of the material that it is purely of vegetable or synthetic origin.			
2. Study of equivalence of the materials and the impact on production of the final material and impact on behaviour (e.g. dissolution characteristics) of the finished product.			

B.II.c.4 Change in synthesis or recovery of a non-pharmacopoeial excipient (when described in the dossier Module 3 / Part II) or a novel excipient	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Minor change in synthesis or recovery of a non-pharmacopoeial excipient or a novel excipient	**1, 2**	**1, 2, 3, 4**	**IA**
b) The specifications are affected or there is a change in the physico-chemical properties of the excipient which may affect the quality of the finished product.			**II**
c) The excipient is a biological / immunological substance			**II**
Conditions			
1. The synthetic route and specifications are identical and there is no change in the qualitative and quantitative impurity profile (excluding residual solvents, provided they are controlled in accordance with ICH/VICH limits), or in physico-chemical properties.			
2. Adjuvants are excluded.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products).			
2. Batch analysis data (in the form of a comparative table) for at least two batches (minimum pilot scale) of the excipient that were manufactured according to the currently approved and proposed processes.			
3. Where appropriate, comparative dissolution profile data for the finished product on at least two batches (minimum pilot scale). For herbal medicinal products, comparative disintegration data may be acceptable.			
4. Copy of approved and new (if applicable) specifications of the excipient.			

B.II.d) Control of finished product

B.II.d.1 Change in the specification parameters and/or limits of the finished product	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Tightening of specification limits	**1, 2, 3, 4**	**1, 2**	**IA**
b) Tightening of specification limits for medicinal products subject to Official Control Authority Batch Release	**1, 2, 3, 4**	**1, 2**	**IA_{IN}**

c) Addition of a new specification parameter with its corresponding test method	**1, 2, 5, 6, 7**	**1, 2, 3, 4, 5, 7**	**IA**
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter such as odour and taste or identification test for a colouring or flavouring material)	**1, 2, 9**	**1, 2, 6**	**IA**
e) Change outside the approved specifications limits range			**II**
f) Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product			**II**
g) Addition or replacement (excluding biological or immunological products) of a specification parameter with its corresponding test method as a result of a safety or quality issue		**1, 2, 3, 4, 5, 7**	**IB**
h) Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur. for the finished product (*)	**1, 2, 3, 4, 7, 8**	**1, 2**	**IA_{IN}**
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)	**1, 2, 10**	**1, 2, 4**	**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 does not result from unexpected events arising during manufacture e.g. new unqualified impurity or change in total impurity limits.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes to the test procedure are minor.
5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.
6. The test method is not a biological / immunological / immunochemical method or a method using a biological reagent for a biological active substance.
7. The change does not concern any impurities (including genotoxic impurities) or dissolution.
8. The change concerns the updating of the microbial control limits to be in line with the current Pharmacopoeia, and the currently registered microbial control limits (present situation) are in line with the pre-January 2008 (non-harmonised) situation and does not include any additional specified controls over the Pharmacopoeia requirements for the particular pharmaceutical form and the proposed controls are in line with the harmonised monograph.
9. The specification parameter or proposal for the specific pharmaceutical form does not concern a critical parameter for example: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the finished product), any critical physical characteristics (hardness or friability for uncoated tablets, dimensions), a test that is required for the particular pharmaceutical form in accordance with the general notices of the Ph. Eur. or any request for skip testing.

10. The proposed control is fully in line with Table 2.9.40.-1 of the Ph. Eur. monograph 2.9.40 and does not include the alternative proposal for testing uniformity of dosage units by mass variation instead of content uniformity when the latter is specified in Table 2.9.40.-1.
Documentation
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products).
2. Comparison of current and proposed specifications.
3. Details of any new analytical method and validation data, where relevant.
4. Batch analysis data for two production batches (three production batches for biologicals, unless otherwise justified) of the finished product for all specification parameters.
5. Where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch complying with the current and proposed specifications. For herbal medicinal products, comparative disintegration data may be acceptable.
6. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.
7. Justification of the new specification parameter and the limits.
* Note: There is no need to notify Swissmedic of an updated monograph in the European Pharmacopoeia or the Pharmacopoeia Helvetica in the case that reference is made to the “current edition” in the dossier of an authorised medicinal product. This variation therefore applies to cases where no reference to the updated monograph of the pharmacopoeia was contained in the dossier and the variation is made to make reference to the updated version.

B.II.d.2 Change in test procedure for the finished product	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Minor changes to an approved test procedure	**1, 2, 3, 4**	**1, 2**	**IA**
b) Deletion of a test procedure if an alternative test procedure is already authorised	**4**	**1**	**IA**
c) Substantial change to, or replacement of, a biological / immunological / immunochemical test method or a method using a biological reagent or replacement of a biological reference preparation not covered by an approved protocol			**II**
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 outdated 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 previously approved test procedure.			
2. No changes have been made to the total impurity limits, and no new unqualified impurities have been detected.			
3. The analytical method essentially remains 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 update of the technical dossier.
Documentation
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary products), including a description of the analytical method, a summary of the validation data and, if applicable, revised specifications for impurities.
11. 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.
* Note: There is no need to notify Swissmedic of an updated monograph of the European Pharmacopoeia in the case that reference is made to the “current edition” in the dossier of an authorised medicinal product.

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 submitted**	**Type**
			II

B.II.e) Container closure system

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

Swissmedic if outside specifications or potentially outside specifications at the end of the approved shelf-life (with proposed action).
4. The remaining product presentations must be adequate for the dosing instructions and treatment duration as mentioned in the information for healthcare professionals.
Documentation
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary products), including revised product information and/or packaging texts as appropriate.
2. Appropriate data on the new packaging (comparative data on permeability e.g. for O2, CO2, 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 pharmacopoeia requirements or legislation on materials and articles intended to come into contact with food (requirements of the "Ordinance of the FDHA on materials and articles intended to come into contact with foodstuffs" (Consumer Goods Ordinance; SR 817.023.21)).
4. A declaration stating 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 the time of implementation and that the available data did not indicate a problem. It should also be confirmed that the studies will be finalised and that data will be provided immediately to Swissmedic 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 three months, and confirmation that these studies will be finalised, and that data will be provided immediately to Swissmedic if outside specifications, or potentially outside specifications, at the end of the approved shelf-life (with proposed action).
6. If applicable, comparison of the current and proposed immediate packaging specifications.
7. Not applicable to Switzerland.
8. Declaration that the remaining pack sizes are consistent with the dosing instructions and duration of treatment as approved in the information for healthcare professionals and are adequate.
Note on B.II.e.1.b: Applicants are reminded that any change which results in a “new pharmaceutical form” requires the submission of an extension application.

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

1. The change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the marketing authorisation application or a type II variation procedure).
2. The change does not result from unexpected events arising during manufacture.
3. Any change should be within the range of currently approved limits.
4. The test procedure remains the same, or changes to 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 CTD format or NTA format for veterinary medicinal products).
2. Comparison of current and proposed specifications.
3. Details of the new analytical method and validation data, where relevant.
4. Batch analysis data on two batches of the immediate packaging for all specification parameters.
5. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.
6. Justification of the new specification parameter and the limits.

B.II.e.3 Change in test procedure for the immediate packaging of the finished product	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Minor changes to an approved test procedure	**1, 2, 3**	**1, 2**	**IA**
b) Other changes to a test procedure (including replacement or addition)	**1, 3, 4**	**1, 2**	**IA**
c) Deletion of a test procedure if an alternative test procedure is already authorised	**5**	**1**	**IA**
Conditions			
1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the previously approved test procedure.			
2. The analytical method essentially remains 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 a biological / immunological substance.			
5. An alternative test procedure is already authorised for the specification parameter, and this procedure has not been added through IA/IAIN notification.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary products), including a description of the analytical method and a summary of the 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 submitted**	**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 administration, 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. It should also be confirmed that these studies will be finalised and that the data will be provided immediately to Swissmedic 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 CTD format or NTA format for veterinary products) ,including a description, detailed drawing and composition of the container closure material, and including revised product information and/or packaging texts as appropriate.			
2. Not applicable to Switzerland.			
3. Revalidation studies have been performed in case of sterile products terminally sterilised. The batch numbers of the batches used in the revalidation 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 variation and time of submission of a type IB variation, and that the available data did not indicate a problem. It should be confirmed that these studies will be finalised and that data will be provided immediately to Swissmedic if outside specifications or potentially outside specification 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 submitted**	**Type**
a) Change in the number of units (e.g. tablets, ampoules) in a pack	**This change should be submitted as a regulatory change A.102**		
1. Change within the range of the currently approved pack sizes			
2. Change outside the range of the currently approved pack sizes			
b) Deletion of pack size(s)	**This change should be submitted as a regulatory change A.103**		
c) Change in the fill weight / fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, including			**II**

biological / immunological parenteral medicinal products.			
d) Change in the fill weight / fill volume of non-parenteral multi-dose (or single-dose, partial use) products		**1, 2, 3**	**IB**
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary products), including revised product information and/or packaging texts as appropriate.			
2. Justification for the new/remaining pack-size, showing that the new/remaining size is consistent with the dosing instructions and duration of treatment as approved in the information for healthcare professionals.			
3. Declaration that stability studies will be conducted in accordance with the relevant guidelines for products where stability parameters could be affected. Data to be reported only if outside specifications (with proposed action).			
Note on B.II.e.5.c) and d): Applicants are reminded that any changes to the dosage strength of the medicinal product require the submission of an extension application.			

B.II.e.6 Change in any part of the (primary) packaging material not in contact with the finished product formulation (such as colour of flip-off caps, colour code rings on ampoules, change of needle shield (different plastic used))	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Change that affects the product information and/or packaging texts	**1**	**1**	**IA_{IN}**
b) Change that does not affect the product information and/or packaging texts	**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 CTD format or NTA format for veterinary products), including revised product information and/or packaging texts as appropriate.			

B.II.e.7 Change in supplier of packaging components or devices (when mentioned in the dossier Module 3 / Part II)	**Conditions to be fulfilled**	**Documentation to be submitted**	**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 components or devices.			
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 CTD format or NTA format for veterinary medicinal products).
2. For devices for medicinal products for human use, proof of CE marking.
3. Comparison 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 submitted**	**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 / immunological 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.			
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			
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products). 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. Where applicable, results of appropriate microbiological testing should be included.			

2. Revised product information and/or packaging texts.
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 changes.
* Note: extrapolation not applicable for biological / immunological medicinal products [1] Pilot scale batches can be accepted with a commitment to verify the shelf-life on production scale batches.

B.II.g) Design space and post approval change management protocol

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 submitted**	**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 CTD format or NTA format for veterinary medicinal products).			

B.II.g.2 Introduction of a post approval change management protocol related to the finished product	**Conditions to be fulfilled**	**Documentation to be submitted**	**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 CTD format or NTA format for veterinary medicinal products).			

B.II.g.3 Deletion of an approved change management protocol related to the finished product	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
	1	**1, 2**	**IA_{IN}**
Conditions			
1. The deletion of the approved change management protocol related to the finished product is not a result of unexpected events or out of specification results during the implementation of the changes described in the protocol and does not have any effect on the already approved information in the dossier.			
Documentation			

1. Justification for the proposed deletion.
2. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary medicinal products).

B.II.g.4 Changes to an approved change management protocol	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Major changes to an approved change management protocol			**II**
b) Minor changes to an approved 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.g.5 Implementation of changes foreseen in an approved change management protocol	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) The implementation of the change requires no further supportive data	**1**	**1, 2, 4**	**IA_{IN}**
b) The implementation of the change requires further supportive data		**1, 2, 3, 4**	**IB**
c) Implementation of a change for a biological/immunological medicinal product		**1, 2, 3, 4, 5**	**IB**
Conditions			
1. The proposed change has been performed fully in line with the approved change management protocol, which requires its immediate notification following implementation.			
Documentation			
1. Reference to the approved change management protocol.			
2. Declaration that the change is in accordance with the approved change management 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 CTD format or NTA format for veterinary medicinal products).			
5. Copy of approved specifications of the finished product.			

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B.II.h Adventitious Agents Safety

B.II.h.1 Update to the "Adventitious Agents Safety Evaluation" information in section 3.2.A.2	Conditions to be fulfilled	Documentation to be submitted	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 the risk assessment			**II**
2. Without modification of the risk assessment		**1, 2, 3**	**IB**
Documentation			
1. Amendment of the relevant section(s) of the dossier 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. Revised product information and/or packaging texts, where applicable.			

1.2.3 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 / or for an excipient	Conditions to be fulfilled	Documentation to be submitted	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**	**IA_{IN}**
2. Updated certificate from an already approved manufacturer	**1, 2, 3, 4, 8**	**1, 2, 3, 4, 5**	**IA**
3. New certificate from a new manufacturer (replacement or addition)	**1, 2, 3, 4, 5, 8, 11**	**1, 2, 3, 4, 5**	**IA_{IN}**
4. Deletion of certificates (if multiple certificates exist for a material)	**10**	**3**	**IA**
5. 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**	**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**	**IA**
3. Updated certificate from an already approved manufacturer	**7, 9**	**1, 2, 3, 4**	**IA**
4. Deletion of certificates (if multiple certificates exist for a 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 requirements) and product-specific requirements (e.g. particle size distribution or 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 substances only: the active substance 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 the material.
8. For herbal preparations: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.
9. If gelatine manufactured from bones is to be used in a medicinal product for parenteral use, it should only be manufactured in compliance with the relevant country requirements.
10. At least one manufacturer for the same material 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 European Pharmacopoeial Certificate of Suitability (CEP), it must not use water during the last steps of the synthesis. If water is used during the last steps of the synthesis, the active substance must also be declared to be free from bacterial endotoxins.
Documentation
1. Copy of the current (updated) Ph. Eur. Certificate of Suitability.
2. If a manufacturing site is added, a comparison of present and proposed manufacturers.
3. Amendment of the relevant section(s) of the dossier (presented in the CTD format) including the updated *Manufacturer information HMV4* form, if applicable.
4. Where applicable, a document providing information of any materials falling within the scope of the current "Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products" (including those 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. In addition an updated *Substances of Animal or Human Origin HMV4* form.
5. Completed and signed form *Declaration by the Responsible Person for foreign manufacturers HMV4*, if applicable.
6. Suitable evidence to confirm compliance of the water used in the final steps of the synthesis of the active substance with the corresponding requirements on quality of water for pharmaceutical use.

B.III.2 Change to comply with Pharmacopoeia Europaea or Pharmacopoeia Helvetica	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Change of specifications of a former non-EU Pharmacopoeial substance to fully comply with the Pharmacopoeia Europaea or Pharmacopoeia Helvetica			
1. Active substance.	**1, 2, 3, 4, 5**	**1, 2, 3, 4**	**IA_{IN}**
2. Excipient / active substance starting material.	**1, 2, 4**	**1, 2, 3, 4**	**IA**
b) Change to comply with an update of the relevant monograph of the Pharmacopoeia Europaea or Pharmacopoeia Helvetica	**1, 2, 4, 5**	**1, 2, 3, 4**	**IA**
c) Change in specifications from the Pharmacopoeia Helvetica to the Pharmacopoeia Europaea	**1, 4, 5**	**1, 2, 3, 4**	**IA**
Conditions			

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1. The change is made exclusively to fully comply with the pharmacopoeia. All the tests in the specification (with the exception of any additional tests) need to correspond to the pharmacopoeial standard after the change.
2. Additional specifications to the pharmacopoeia for product-specific properties are unchanged (e.g. particle size distribution, polymorphic form or e.g. bioassays, aggregates).
3. No significant changes in the 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 preparations: 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 CTD format or NTA format for veterinary medicinal products).
2. Comparison of current and proposed specifications.
3. Batch analysis data (in a comparative tabulated format) for 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 those listed in the monograph.
Note: There is no need to notify Swissmedic of an updated monograph of the European Pharmacopoeia or Pharmacopoeia Helvetica in the case that reference is made to the ‘current edition’ in the dossier of an authorised medicinal product.

1.2.4 B.IV. Medical devices

B.IV.1 Change of a measuring or administration device	Conditions to be fulfilled	Documentation to be submitted	Type
a) Addition or replacement of a device which is not an integral 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 devices 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 integral 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 dosage instructions, and the results of corresponding studies must be available.			
2. The new device must be compatible with the medicinal product.			
3. The change should not lead to substantial amendments of the product information and/or packaging texts.			
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 medical device is not used as a solvent of the medicinal product.			
7. If a measuring function is intended, the CE marking should also cover the measuring function.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary products), including description, detailed drawing and composition of the device material and supplier where appropriate, and including revised product information and/or packaging texts 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 the accuracy, precision and compatibility of the device.			
4. Not applicable to Switzerland.			
5. Justification for the deletion of the device.			
Note on B.IV.1.c: Applicants are reminded that any change which results in a “new pharmaceutical form” requires the submission of an extension application.			

B.IV.2 Change in specification parameters and/or limits of a measuring or administration device for veterinary medicinal products	Conditions to be fulfilled	Documentation to be submitted	Type
a) Tightening of specification limits.	**1, 2, 3, 4**	**1, 2**	**IA**
b) Addition of a new specification parameter 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 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.			
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 CTD format or NTA format for veterinary medicinal products).			
2. Comparison of current and proposed specifications.			
3. Details of any new analytical method and summary of the validation data.			
4. Batch analysis data on two production batches for all tests in the new specification.			
5. Justification/risk assessment showing that the parameter is non-significant or that it is obsolete.			
6. Justification of the new specification parameter and the limits.			

B.IV.3 Change in the test procedure of a measuring or administration device for veterinary medicinal products	**Conditions to be fulfilled**	**Documentation to be submitted**	**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 previously approved 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/IAIN notification.			
Documentation			

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1. Amendment of the relevant section(s) of the dossier (presented in the CTD format or NTA format for veterinary products), including a description of the analytical method and a summary of the 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.

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1.3 C. Safety, efficacy and pharmacovigilance changes

1.3.1 C.I. Human and veterinary medicinal products

C.I.1 Change in the product information and/or packaging texts intended to implement the outcome of a Swissmedic administrative procedure:	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) The medicinal product is covered by the defined scope of the procedure.	**1**	**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 is required to be submitted by the marketing authorisation holder.		**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 marketing authorisation holder.		**1, 3**	**II**
Conditions			
1. The wording required by Swissmedic is implemented with the variation, but the submission of additional information and/or further assessment is not required.			
Documentation			
1. Attached to the variation application is a reference to the relevant official decision together with the product information and/or packaging texts.			
2. Declaration that the proposed product information and/or packaging texts are identical, in the sections concerned, to the corresponding texts attached to the official decision.			
3. Revised product information and/or packaging texts.			

C.I.2 Change in the product information and/or packaging texts for a medicinal product with a known active substance with/without innovation, biosimilar or preparation for parallel import following assessment of the same change for the reference medicinal product / reference preparation	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Implementation of one or more changes for which no new additional data is required to be submitted by the marketing authorisation holder.	**1, 2**	**1, 2**	**IA_{IN}**
b) Implementation of one or more changes which require to be substantiated by the submission of new additional data (e.g. comparability) by the marketing authorisation holder.			**II**
Conditions			
1. The product information for the medicinal product is identical, in the sections affected by the change, to that for the reference medicinal product / reference preparation.			
2. If applicable, passages for the reference medicinal product / reference preparation connected with document protection are deleted (in Track Changes mode).			

Documentation
1. Not applicable to Switzerland.
2. Revised product information and/or packaging texts.

C.I.3 Change in the product information and/or packaging texts intended to implement the outcome of a procedure concerning Periodic Safety Update Reports (PSUR) or Post Authorisation Safety Studies (PASS)	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Implementation of the wording agreed with Swissmedic	**1**	**1, 2**	**IA_{IN}**
b) Implementation of one or more changes that require to be substantiated by the submission of new additional data by the marketing authorisation holder		**2**	**II**
Conditions			
1. The wording required by Swissmedic is implemented with the variation, but the submission of additional information and/or further assessment is not required.			
Documentation			
1. A reference to the relevant official decision should be attached to the variation application.			
2. Revised product information and/or packaging texts.			

C.I.4 Change in the product information and/or packaging texts due to new quality, preclinical, clinical or pharmacovigilance data[2]	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
			II

C.I.5 Change in the dispensing category	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) For a medicinal product with a known active substance without innovation or a biosimilar after an approved change in the legal category for the reference product		**2**	**IB**
b) For all other medicinal products		**1, 2**	**II**
Documentation			
1. Scientific documentation.			
2. Revised product information and/or packaging texts.			

C.I.6 Change to therapeutic indication(s)	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) Addition of a new therapeutic indication or modification of an approved one		**1, 2, 3, 4**	**II**
b) Deletion of a therapeutic indication		**4**	**IB**
Documentation			
1. Quality: If applicable, supplemented Section 3.2.P together with a change index and tabular comparison.			

[2] C.I.101 applies to changes in the product information and/or packaging texts due to new dosage recommendation data.

2. Preclinical: - Section 2.4 supplemented with critical, safety-related points. - Benefit/risk analysis for the new indication. As a rule, new experimental trials must be submitted for newly identified risks or extension of the duration of use. These should be summarised accordingly in Section 2.6 and the studies incorporated in Module 4. If new populations are involved, specific non-clinical studies and corresponding dose-finding studies should be considered.

3. Clinical: Studies on efficacy and safety for the new indication(s)
- Pharmacokinetic studies (PK) (Sections 5.3.1 and 5.3.3) (if applicable), for example
  - Investigation of PK in specific populations that were not investigated for the primary indication (Section 5.3.3.3).
  - Investigation of PK in patients for the new proposed indication(s) (Section 5.3.3.2) (e.g. if the organ system for which the product's new indication is intended is difference from the primary organ systems treated with the product).
  - additional interaction studies on population kinetics (Section 5.3.3.5).
- Pharmacodynamic (PD) studies (Section 5.3.4)
  - Investigation of the mechanism of action in the new proposed indication(s).
  - PK/PD analyses to determine the effective concentration where appropriate.
- Studies on efficacy and safety (Section 5.3.5)
  - Dose-finding studies or appropriate justification as to why the dosage to date is also appropriate for the new indication(s).
  - Studies on the efficacy and safety of the new proposed indications, including specific, indication-related studies, e.g. long-term studies.
  - Pooled analysis of the Phase III (and Phase II) data where appropriate.
- If the new indication is linked to a new dosage strength and/or dosage recommendation, see also the requirements for documentation on C.I.101 Change in the product information and/or packaging texts due to new dosage recommendation data and/or on extension 2.c) Change or addition of a new dosage strength/potency.

4. Revised product information.

C.I.7 Deletion	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
a) A pharmaceutical form		**1, 2**	**IB**
b) A dosage strength		**1, 2**	**IB**
Documentation			
1. Declaration that the remaining product presentations conform to the dosage instructions and treatment duration included in the information for healthcare professionals.			
2. Revised product information and/or packaging texts.			

C.I.8 – C.I.11: not applicable to Switzerland

C.I.12 Inclusion or deletion of the black triangle and inclusion or deletion of explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
	1	**1, 2**	**IA_{IN}[3]**
Conditions			

[3] This variation covers the situation where the inclusion or deletion of the black triangle or explanatory statements is not done as part of another procedure (e.g. a renewal or variation procedure connected with the product information).

1. The medicinal product is included in, or deleted from, the list of medicinal products that are subject to additional monitoring.
Documentation
1. A reference to the list of medicinal products that are subject to additional monitoring is attached to the variation application.
2. Revised product information and/or packaging texts.

C.I.13 Other variations relating to safety, efficacy and pharmacovigilance that require the submission of studies to Swissmedic	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
			II

C.I.100 Safety-related change in the product information and/or packaging texts due to new quality, preclinical, clinical or pharmacovigilance data	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
			II

C.I.101 Change in the product information and/or packaging texts due to new dosage recommendation data	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
		1, 2, 3	**II**
Documentation			
1. Quality: If applicable, supplemented Section 3.2.P together with a change index and tabular comparison.			
2. Preclinical: - Section 2.4 supplemented with critical safety-related points. - Benefit/risk analysis relating to the new dosage recommendation, taking particular account of the safety margins.			
3. Clinical: - The requirements depend on the type of variation. Normally, corresponding studies on efficacy and safety (Section 5.3.5) should be submitted, including specific studies depending on the indication, e.g. long-term studies. For higher dosages, the focus must be on safety, whereas for lower dosages it must be on efficacy. Additional data on safety pharmacology may also be required, in particular for doses higher than those previously recommended. - If the only change concerns the dosing interval, PK bridging or PD bridging may be sufficient.			

C.I.102 Extension of the document protection for additional indications	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
	1, 2, 3	**1**	**II**
Conditions			
1. This involves a new indication with a document protection period of three years.			
2. The new indication provides significant clinical benefit compared to existing treatments.			
3. The new indication is supported by comprehensive clinical trials.			
Documentation			

1. Conclusive proof that a significant therapeutic improvement exists: It can be demonstrated, on the basis of comprehensive clinical trial data, that the benefit-risk profile in an indication is significantly improved compared to the existing therapeutic options.

C.I.103 Document protection for purely paediatric use	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
	1, 2, 3		**IB**
Conditions			
1. The medicinal product is specifically and exclusively intended for paediatric use.			
2. Document protection has not yet been granted for any other medicinal product authorised by Swissmedic with the same active substance for the same specific paediatric use.			
3. The studies submitted for authorisation conform to the approved paediatric investigation plan according to Article 54a TPA, and all measures for the proposed population from the paediatric investigation plan are fulfilled.			

C.I.104 Document protection for important medicinal products for rare diseases (ODS/MUMS)	**Conditions to be fulfilled**	**Documentation to be submitted**	**Type**
	1, 2		**IB**
Conditions			
1. The medicinal product has been granted Orphan Drug or MUMS status by Swissmedic.			
2. Document protection has not yet been granted for any other medicinal product authorised by Swissmedic with the same active substance for the same use.			

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(Art. 22a)

1.3.2 C.II. Veterinary medicinal product – Specific changes

C.II.1 Modification or addition of a non-food producing target species (pet)	Conditions to be fulfilled	Documentation to be submitted	Type
			II

C.II.2 Deletion of a target animal species (pet or livestock):	Conditions to be fulfilled	Documentation to be submitted	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 and/or packaging texts.			

C.II.3 Change to the withdrawal period for a veterinary medicinal product	Conditions to be fulfilled	Documentation to be submitted	Type
			II

C.II.4 – C.II.5: not applicable to Swissmedic

C.II.6 b) Changes to the labelling or the package leaflet which are not connected with the product information	Conditions to be fulfilled	Documentation to be submitted	Type
		1	IB
Documentation			
1. Revised product information and/or packaging texts.			

C.II.100 Change in a veterinary medicinal product authorised in the notification procedure	Conditions to be fulfilled	Documentation to be submitted	Type
	1	1	IB
Conditions			
1. The variation concerns an entry made on the latest *New authorisation variation in notification procedure VMP HMV4* form.			
Documentation			
1. Updated *New authorisation variation in notification procedure VMP HMV4* form.			

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(Art. 22a)

1.4 X. Changes to PMF

X. Changes to PMF	Conditions to be fulfilled	Documentation to be submitted	Type
a) Type IA_{IN} (according to EU D. PMF/VAMF)	**1**	**1, 2**	**IA_{IN}**
b) Type IA (according to EU D. PMF/VAMF)	**1**	**1, 2**	**IA**
c) Type IB (according to EU D. PMF/VAMF)	**1**	**1, 2**	**IB**
d) Type II (according to EU B.V.a.1 PMF/VAMF or D. PMF/VAMF)			
1. First-time inclusion of a new Plasma Master File (EU B.V.a.1a)	**1**	**1, 2**	**II**
2. Other type II variation (EU D. PMF/VAMF)	**1**	**1, 2**	**II**
Conditions			
1. The application for each PMF for one or more PMF changes is submitted according to the highest category according to the classification in the European Guideline under "B.V.a.1 PMF/VAMF" or "D. PMF/VAMF".			
Documentation			
1. Amendment of the relevant section(s) of the dossier.			
2. Comparison of currently approved situation and proposed changes.			

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(Art. 22a)

1.5 Y. Change in the reduced dossier for complementary medicines

Y.1 Change in the reduced dossier	Conditions to be fulfilled	Documentation to be submitted	Type
	1	**1**	**IB**
Conditions			
1. See Complementary and Phytotherapeutic Products Ordinance (KPTPO)			
Documentation			
1. See KPTPO annex 3			

Y.2 Change in the company's basic dossier	Conditions to be fulfilled	Documentation to be submitted	Type
a) For complementary medicinal products managed in HOMANT	**1**	**1**	**IB**
b) For complementary medicinal products managed in HOMANT Asia	**1**	**1**	**IB**
c) For individual teas, cough and throat lozenges and pastilles as per Art. 15 para. 1b TPA	**1**	**1**	**IB**
Conditions			
1. The variation concerns an entry made on the latest *New authorisation variation in notification procedure KPTPO HMV4* form.			
Documentation			
1. Updated *New authorisation variation in notification procedure KPTPO HMV4* form.			

Y.3 Change in the Master dossier	Conditions to be fulfilled	Documentation to be submitted	Type
	1	**1**	**IB**
Conditions			
1. The variation concerns an entry made on the latest *New authorisation variation in notification procedure KPTPO HMV4* form.			
Documentation			
1. Updated *New authorisation variation in notification procedure KPTPO HMV4* form.			

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1.6 Z. Extensions

1.	**Change in the active substance:**
	a) Replacement of a chemical active substance by a different salt/ester complex/derivative with the same therapeutic moiety, where the efficacy/safety characteristics are not significantly different.
	b) Replacement by a different isomer, a different mixture of isomers, of a mixture by an isolated isomer (e.g. racemate by a single enantiomer), where the efficacy/safety characteristics are not significantly different.
	c) Replacement of a biological active substance with one of a slightly different molecular structure where the efficacy/safety characteristics are not significantly different, with the exception of: changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza
	d) Modification of the vector used to produce the antigen or the source material, including a new master cell bank from a different source, where the efficacy/safety characteristics are not significantly different.
	e) A new ligand or coupling mechanism for a radiopharmaceutical, where the efficacy/safety characteristics are not significantly different.
	f) Major change to the extraction solvent or the ratio of herbal drug to herbal drug preparation where the efficacy/safety characteristics are not significantly different.
2.	**Change in dosage strength, pharmaceutical form or administration route:**
	a) Change of bioavailability.
	b) Change of pharmacokinetics, e.g. change in rate of release.
	c) Change or addition of a new dosage strength/potency.
	d) Change or addition of a new pharmaceutical form.
	e) Change or addition of a new route of administration.[4]
3.	**Other change specific to veterinary medicinal products: Change or addition of a food-producing target species (livestock)**

[4] For parenteral administration, it is necessary to distinguish between intra-arterial, intravenous, intramuscular, subcutaneous and other routes.

For administration to poultry, respiratory, oral and ocular (nebulisation) routes used for vaccination are considered to be equivalent routes of administration.

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