the letter of medibridge
Regulatory Affairs
number 26
January 2012

New regulation related to variations

Focus on the active substance

editorial

The application of the new regulation related to variations is mandatory since 1st January 2010 for centralised, mutual recognition and decentralised procedure applications.

However, its implementation and the definition of the positioning of some variations still raises questions from the pharmaceutical industry. In addition, regulatory affairs professionals have to simultaneously juggle this new regulation and the national regulation, as the new regulation has not yet been implemented throughout Europe.

To facilitate respect of this new regulation in practice, we propose to edit, in several issues of the Letter of Medibridge, the content of the guideline (2010/C 17/01) published in 2010.

As in previous Letters, we aim to provide here a synthetic tool for determining the positioning of your applications for modifications related to the active substance.

As always, this document should be considered to be the work of individuals. We advise you to also refer to the published official texts and guidelines in force.

Saholy RAKOTOMANGA
Director of Pharmaceutical Affairs

Introduction

The European Commission Regulation (EC) no.1234/2008 of 24 November 2008 introduced new rules for the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products. The provisions of this Regulation have been applicable since 1st January 2010 to medicinal products authorised *via* the Centralised, Decentralised and Mutual Recognition Procedures.

The same three variation categories (type IA, IB and II) as before are still described in this new Regulation, but several changes have been introduced. For example, Type IA variations are now called "Do and Tell" variations and are divided into two sub-categories: type IA variations (which must be submitted within one year following their implementation), and type IA_{IN} variations (which must be submitted immediately after their implementation).

This new Regulation has also changed the concept of classifying variations "by default":

- when modifications are neither extensions nor classified as type IA or type II variations in the Guideline, or
- when the conditions required for classification as a type IA variation are not met and the change is not specifically listed as a type II variation,

these modifications are now classified as type IB by default (except if they have an impact on Quality, Safety or Efficacy, in which case they must be classified as type II variations).

Moreover, the concepts of Grouping and Worksharing have been created through this new Regulation, to simplify the evaluation procedure to groups of variations related to one or more of marketing authorisation(s) belonging to the same marketing authorisation holder (MAH).

Following the entry into force of this new Regulation, a Guideline detailing the various categories of variations to the term of marketing authorisations for medicinal products for human use and veterinary products (2010/C 17/01) was published in the Official Journal of the European Union on 22 January 2010.

This Guideline classifies modifications according to the following scheme, and stipulates the conditions to be respected as well as the documentation to be provided:

A. ADMINISTRATIVE CHANGES

B. QUALITY CHANGES
- **I. Active Substance**
- **II Finished Product**
- **III. CEP/TSE/monographs**
- **IV. Medical Devices**
- **V. Changes to a marketing authorisation resulting from other regulatory procedures**

C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES
- **I. Human and Veterinary medicinal products**
- **II. Veterinary medicinal product - specific changes**

D. PMF/VAMF

When classification of a proposed modification is not feasible using this Guideline, the MAH can request advice from the CMD(h), according to Article 5 of the new Regulation. Additional modifications, classified by the CMD(h) according to Article 5, are described in the document "Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) no. 1234/2008", published on the CMD(h) website and regularly updated. This document should be consulted in conjunction with the Guideline, to determine the appropriate classification of the proposed modification.

The present Letter of MediBridge will focus only on administrative and quality changes related to the active substance, as defined in the Guideline. The additional classifications of the CMD(h), according to Article 5, where applicable, are announced by the following illustration :

Art 5

A. ADMINISTRATIVE CHANGES

A.3 Change in the name of the active substance	Procedure Type IA_{IN}
Conditions: 1. The active substance shall remain the same. 2. For veterinary medicinal products for food-producing species, the new name has been published in Regulation (EC) No 470/2009 before implementation of this change.	

A.4 Change in the name and/or address of a manufacturer (including where relevant quality control sites) or supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the product dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier	Procedure Type IA
Condition: 1. The manufacturing site and all manufacturing operations shall remain the same.	

A.6 Change in ATC Code / ATC Vet Code	Procedure Type IA
Condition: 1. Change following granting of or amendment to ATC Code by WHO / ATC Vet Code.	

A.7 Deletion of manufacturing sites (including for an active substance, intermediate or finished product, packaging site, manufacturer responsible for batch release, site where batch control takes places, or supplier of a starting material, reagent or excipient (when mentioned in the dossier)	Procedure Type IA
Conditions: 1. There should at least remain one site/manufacturer, as previously authorised, performing the same function as the one(s) concerned by the deletion. 2. The deletion should not be due to critical deficiencies concerning manufacturing.	

B. QUALITY CHANGES

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 sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier	Procedure Type
a) The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	IA_{IN}
Conditions: 1. For starting materials and reagents, the specifications (including in process controls, methods of analysis of all 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 not a biological/immunological substance or sterile. 3. Where materials of human or animal origin are used in the 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.*	
b) Introduction of a new manufacturer of the active substance that is supported by an ASMF	II
No condition	
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
No condition	
d) New manufacturer of material for which an assessment is required of viral safety and/or TSE risk	II
No condition	
e) The change relates to a biological active substance or a starting material/reagent/intermediate used in the manufacture of a biological/immunological product	II
No condition	
f) Changes to quality control testing arrangements for the active substance-replacement or addition of a site where batch control/testing takes place	IA
Conditions: 2. The active substance is not a biological/immunological substance or sterile. 4. Method transfer from the old to the new site has been successfully completed.	

Art 5

B.I.a.1.z): Addition of an alternative sterilisation (gamma irradiation) site for the active substance - proposed classification: IB.

Note:

- *The case of groupings including modification B.1.a.1 is discussed in the document "Examples for acceptable and not acceptable groupings for MRP/DCP products" published by CMD(h). Please refer to page 8 of this Letter.*
- *Variations B.1.a.1.c) to e) are listed as type II and correspond to variations for which at least one of the conditions 1, 2 or 3 are not fulfilled.*

B.I.a.2 Changes in the manufacturing process of the active substance	Procedure Type
a) Minor change in the manufacturing process of the active substance	IA
Conditions: 1. No adverse change in qualitative and quantitative impurity profile or in physico-chemical properties. 2. The synthetic route remains the same, *i.e.* intermediates remain the same and there are no new reagents, catalysts or solvents used in the process. In the case of herbal medicinal products, the geographical source, production of the herbal substance and the manufacturing route remain the same. 3. The specifications of the active substance or intermediate are unchanged. 4. The change is fully described in the open ("applicant's") part of an Active Substance Master File, if applicable. 5. The active substance is not a biological/immunological substance. 6. The change does not refer to the geographical source, manufacturing route or production of a herbal medicinal product. 7. The change does not refer to the restricted part of an Active Substance Master File.	
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 medicinal product	II
No condition	
c) The change refers to a biological/immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	II
No condition	
d) The change relates to a herbal medicinal product and there is a change to any of the following: geographical source, manufacturing route or production	II
No condition	
e) Minor change to the restricted part of an Active Substance Master File	IB
No condition	

B.I.a.3 Change in batch size (including batch size ranges) of active substance or intermediate	Procedure Type
a) Up to 10-fold increase compared to the currently approved batch size	IA
Conditions: 1. Any changes to the manufacturing methods areonly 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 concerned is not a biological/immunological medicinal product. 4. The change does not adversely affect the reproducibility of the process. 6. The specifications of the active substance/intermediates remain the same. 7. The active substance is not sterile. 8. The currently approved batch size was not approved *via* a Type IA variation.	
b) Downscaling	IA
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 concerned 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.	
c) The change requires assessment of the comparability of a biological/immunological active substance	II
No condition	
d) More than 10-fold increase compared to the currently approved batch size	IB
No condition	
e) The scale for a biological/immunological active substance is increased/decreased without process change (*e.g.* duplication of line)	IB
No condition	

Note:

- *The conditions to be fulfilled described in the Guideline for variation B.I.a.2.a) allow to clearly define a "minor" change. Anyway, it must be pointed out that these conditions are redundant: condition 6 corresponds to the second part of condition 2, condition 7 is the corollary of condition 4.*
- *A note, specific to variation B.I.a.2.b), is introduced in order to define the "substantial" change: change to the synthetic route or manufacturing conditions, which may have a potential to change important quality characteristics of the active substance, such as qualitative and/or quantitative impurity profile requiring qualification, or physico-chemical properties impacting on bioavailability.*
- *Variations B.I.a.2.b) to d) are listed as type II and correspond to variations for which at least one of the conditions 1 to 7 are not fulfilled.*
- *Variation B.I.a.2.e) is listed as a type IB and corresponds to a minor change in the restricted part of an Active Substance Master File (ASMF). An additional document is required to support this variation: declaration from the MAH or the ASMF holder that:*
  - *there is no change in qualitative and quantitative impurity profile or in physico-chemical properties,*
  - *the synthetic route remains the same,*
  - *the specifications of the active substance or intermediates are unchanged.*

Note:

- *Condition no. 8 avoids authorisation of a substantial increase in batch size solely on the basis of several successive type IA variation applications.*

B.I.a MANUFACTURE (continued)

B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance	Procedure Type
a) Tightening of in-process limits	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). 2. The change does not result from unexpected events arising during manufacture *e.g.* new unqualified impurity; 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 in the test procedure are minor.	
b) Addition of a new in-process test and limits	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). 2. The change does not result from unexpected events arising during manufacture *e.g.* new unqualified impurity; change in total impurity limits. 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).	
c) Deletion of a non-significant in-process test	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). 2. The change does not result from unexpected events arising during manufacture *e.g.* new unqualified impurity; change in total impurity limits.	
d) Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the active substance	II
No condition	
e) Deletion of an in-process test which may have a significant effect on the overall quality of the active substance	II
No condition	
f) Addition or replacement of an in-process test as a result of a safety or quality issue	IB
No condition	

B.I.a.5 Changes to the active substance of a seasonal, pre-pandemic or pandemic vaccine against human influenza	Procedure Type
a) Replacement of the strain(s) in a seasonal, pre-pandemic or a pandemic vaccine against human influenza	II
No condition	

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	Procedure Type
a) Tightening of specification limits for medicinal products subject to Official Batch Release	IA_{IN}
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; 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 in the test procedure are minor.	
b) Tightening of specification limits	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). 2. The change does not result from unexpected events arising during manufacture *e.g.* new unqualified impurity; 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 in the test procedure are minor.	
c) Addition of a new specification parameter to the specification with its corresponding test method	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). 2. The change does not result from unexpected events arising during manufacture *e.g.* new unqualified impurity; change in total impurity limits. 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 pharmacopoeia microbiological methods). 7. The change does not concern a genotoxic impurity.	
d) Deletion of a non-significant specification parameter (*e.g.* deletion of an obsolete parameter)	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). 2. The change does not result from unexpected events arising during manufacture *e.g.* new unqualified impurity; change in total impurity limits.	
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
No condition	
f) Change outside the approved specifications limits range for the active substance	II
No condition	
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
No condition	
h) Addition or replacement (excluding biological or immunological substance) of a specification parameter as a result of a safety or quality issue	IB
No condition	

B.I.b.2 Change in test procedure for active substance or starting material/reagent/ intermediate used in the manufacturing process of the active substance	Procedure Type
a) Minor changes to an approved test procedure	IA
Conditions: 1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure. 2. There have been no changes of the total impurity limits; no new unqualified impurities are detected. 3. The method of analysis should remain the same (*e.g.* a change in column length or temperature, but not a different type of column or method). 4. The test method is not a biological/immunological/immunochemical method, or a method using a biological reagent for a biological active substance (does not include standard pharmacopoeial microbiological methods).	
b) Deletion of a test procedure for the active substance or a starting material/reagent intermediate, if an alternative test procedure is already authorised	IA
Condition: 7. An alternative test procedure is already authorised for the specification parameter and this procedure has not been added through IA/IA_{IN} notification.	
c) Other changes to a test procedure (including replacement or addition) for a reagent, which does not have a significant effect on the overall quality of the active substance	IA
Conditions: 1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure. 2. There have been no changes of the total impurity limits; no new unqualified impurities are detected. 3. The method of analysis should remain the same (*e.g.* a change in column length or temperature, but not a different type of column or method). 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 biological/immunological.	
d) Change (replacement) to a biological/immunological/ immunochemical test method or a method using a biological reagent for a biological active substance. *e.g.* peptide map, glyco-map, etc.	II
No condition	
e) Other changes to a test procedure (including replacement or addition) for the active substance or a starting material/intermediate	IB
No condition	

Art 5

B.I.b.z): Removal of the approved level of testing performed by the finished product manufacturer on receipt of the drug substance batches - proposed classification: IB.

General Note for B.I.c variations:

- *Modifications related to the packaging of the active substance were not specifically described in the former guideline. This type of variation is a typical innovation of the new regulation.*
- *It must be pointed out that the level of information supplied on the container closure system seems very detailed in comparison with the usual content of the pharmaceutical file.*

B.1.c.1. Change in immediate packaging of the active substance	Procedure Type
a) Qualitative and/or quantitative composition	IA
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 conditions and relevant stability parameters have been assessed in at least two pilot scale or industrial scale batches and at least three months satisfactory stability data are at the disposal of the applicant at time of implementation. However, if the proposed packaging is more resistant than the existing packaging, the three months' stability data do not yet have to be available. These studies must be finalised and the data will be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the shelf-life/retest period (with proposed action). 3. Sterile, liquid and biological/immunological active substances are excluded.	
b) Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological active substances	II
No condition	
c) Liquid active substances (non sterile)	IB
No condition	

Note:

- *Variations B.1.c.1.b) and B.1.c.1.c) are listed as type II and type IB, respectively, as the condition 3 is not fulfilled.*

B.I.c CONTAINER CLOSURE SYSTEM (continued)

B.I.c.2 Change in the specification parameters and/or limits of the immediate packaging of the active substance	Procedure Type
a) Tightening of specification limits	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 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 in the test procedure are minor.	
b) Addition of a new specification parameter to the specification with its corresponding test method	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 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. 5. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way.	
c) Deletion of a non-significant specification parameter (*e.g.* deletion of an obsolete parameter)	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 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.	
d) Addition or replacement of a specification parameter as a result of a safety or quality issue	IB
No condition	

B.I.c.3 Change in test procedure for the immediate packaging of the active substance	Procedure Type
a) Minor changes to an approved test procedure	IA
Conditions: 1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure. 2. The method of analysis should remain the same (*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.	
b) Other changes to a test procedure (including replacement or addition)	IA
Conditions: 1. Appropriate validation studies have been performed in accordance with the relevant guidelines and show that the updated test procedure is at least equivalent to the former test procedure. 3. Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way. 4. The active substance/finished product is not biological/immunological.	
c) Deletion of a test procedure if an alternative test procedure is already authorised	IA
Condition: 5. There is still a test procedure registered for the specification parameter and this procedure has not been added through a IA/IA_{IN} notification.	

B.I.d. STABILITY

B.I.d.1 Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. Certificate of Suitability covering the retest period is part of the approved dossier	Procedure Type
a) Re-test period/storage period	
1. Reduction	IA
Condition: 1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.	
2. Extension of the retest period based on extrapolation of stability data not in accordance with ICH guidelines (*)	II
No condition	
3. Extension of storage period of a biological/immunological active substance not in accordance with an approved stability protocol	II
No condition	
4. Extension or introduction of a re-test period/storage period supported by real time data	IB
No condition	
b) Storage conditions	
1. Change to more restrictive storage conditions of the active substance	IA
Condition: 1. The change should not be the result of unexpected events arising during manufacture or because of stability concerns.	
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
No condition	
3. Change in storage conditions of the active substance	IB
No condition	

(*): retest period not applicable for biological/immunological active substance.

Art 5

B.I.d.z): Deletion of tests or reduction in the frequency of testing in a previously approved stability protocol of the active substance - proposed classification : IB.

Art 5

B.I.d.1.b): Change in storage conditions of the reference standard. The same principles will apply as outlined for the active substance.

B.I.e. DESIGN SPACE

General Note for B.I.e variations:

- *Modifications related to the design space were not specifically described in the previous guideline. This type of variation is a typical innovation of the new regulation.*

B.I.e.1. Introduction of a new design space or extension of an approved design space for the active substance, concerning:	Procedure Type
a) One unit operation in the manufacturing process of the active substance including the resulting in-process controls and/or test procedures	II
No condition	
b) Test procedures for starting materials/reagents/ intermediates and/or the active substance	II
No condition	

B.I.e.2 Introduction of a post approval change management protocol related to the active substance	Procedure Type II
No condition	

B.I.e.3 Deletion of an approved change management protocol related to the active substance	Procedure Type IA_{IN}
Condition: 1. The deletion of the approved change management protocol related to the active substance is not a result of unexpected events or out of specification results during the implementation of the change(s) described in the protocol.	

B.III. CEP / TSE / MONOGRAPHS

B.III.1 Submission of a new or updated Ph. Eur. Certificate of Suitability: **• for an active substance** **• for a starting material/reagent intermediate used in the manufacturing process of the active substance** **• for an excipient**	Procedure Type
a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph	
1. New certificate from an already approved manufacturer	IA_{IN}
Conditions: 1. The finished product release and end of shelf life specifications remain the same. 2. Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and product specific requirements (*e.g.* particle size profiles, polymorphic form), if applicable. 3. The manufacturing process of the active substance, starting material/reagent/ intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required. 4. For active substance only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier. 5. The active substance/starting material/reagent/intermediate/excipient is not sterile. 8. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.	
2. Updated certificate from an already approved manufacturer	IA
Conditions: 1. The finished product release and end of shelf life specifications remain the same. 2. Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and product specific requirements (*e.g.* particle size profiles, polymorphic form), if applicable. 3. The manufacturing process of the active substance, starting material/reagent/ intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required. 4. For active substance only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier. 8. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.	
3. New certificate from a new manufacturer (replacement or addition)	IA_{IN}
Conditions: 1. The finished product release and end of shelf life specifications remain the same. 2. Unchanged (excluding tightening) additional (to Ph. Eur.) specifications for impurities (excluding residual solvents, provided they are in compliance with ICH/VICH) and product specific requirements (*e.g.* particle size profiles, polymorphic form), if applicable. 3. The manufacturing process of the active substance, starting material/reagent/ intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required. 4. For active substance only, it will be tested immediately prior to use if no retest period is included in the Ph. Eur. Certificate of Suitability or if data to support a retest period is not already provided in the dossier. 5. The active substance/starting material/reagent/intermediate/excipient is not sterile. 8. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.	
b) European Pharmacopoeial TSE Certificate of Suitability for an active substance/starting material/reagent/ intermediate/or excipient	
1. New certificate for an active substance from a new or an already approved manufacturer	IA_{IN}
Conditions: 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. 6. The substance is not included in a veterinary medicinal product for use in animal species susceptible to TSE.	
2. New certificate for a starting material/reagent/ intermediate/ or excipient from a new or an already approved manufacturer	IA
Conditions: 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. 6. The substance is not included in a veterinary medicinal product for use in animal species susceptible to TSE.	
3. Updated certificate from an already approved manufacturer	IA
Condition: 7. For veterinary medicinal products: there has been no change in the source of material.	

B.III. CEP / TSE / MONOGRAPHS (Continued)

B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State	Procedure Type
a) Change of specification(s) of a former non Pharmacopoeial substance to comply with the Ph. Eur. or with a national pharmacopoeia of a Member State	
1. Active substance	IA_{IN}
Conditions: 1. The change is made exclusively to comply with the pharmacopoeia. 2. Additional specifications to the pharmacopoeia for product specific properties are unchanged (*e.g.* particle size profiles, polymorphic form or *e.g.* bioassays, aggregates). 3. No significant changes in qualitative and quantitative impurities profile unless the specifications are tightened. 4. Additional validation of a new or changed pharmacopoeial method is not required. 5. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.	
2. Excipient/active substance starting material	IA
Conditions: 1. The change is made exclusively to comply with the pharmacopoeia. 2. Additional specifications to the pharmacopoeia for product specific properties are unchanged (*e.g.* particle size profiles, polymorphic form or *e.g.* bioassays, aggregates). 4. Additional validation of a new or changed pharmacopoeial method is not required.	
b) Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	IA
Conditions: 1. The change is made exclusively to comply with the pharmacopoeia. 2. Additional specifications to the pharmacopoeia for product specific properties are unchanged (*e.g.* particle size profiles, polymorphic form or *e.g.* bioassays, aggregates). 4. Additional validation of a new or changed pharmacopoeial method is not required. 5. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.	
c) Change in specifications from a national pharmacopoeia of a Member State to the Ph. Eur.	IA
Conditions: 1. The change is made exclusively to comply with the pharmacopoeia. 4. Additional validation of a new or changed pharmacopoeial method is not required. 5. For herbal active substances: the manufacturing route, physical form, extraction solvent and drug extract ratio (DER) should remain the same.	

Art 5

B.III.2.z): Compliance with the Ph. Eur. and removal of reference to the internal test method and test method number - proposed classification: IA.

Things to know:

Grouping the introduction of a new manufacturing site with other changes such as changes in batch size, changes in batch releaser and controller, changes in the manufacturing process, etc. is an acceptable grouping, as long as these changes are covered by Annex III point 6 of Regulation 1234/2008: "All variations in the group relate to a project intended to improve the manufacturing process and the quality of the medicinal product concerned or its active substance(s)".

However, still according to this document from CMD(h), the following cases are considered as not acceptable groupings:

- *Introduction of a new active substance manufacturer with a new ASMF grouped with other unrelated quality changes concerning the active substance or the finished product.*
- *Inclusion of a new active substance manufacturer as part of a variation to introduce a new finished product manufacturer.*
- *Addition or change of several active substance manufacturers that do not fully meet the Type IA conditions and documentation requirements.*

Update of an ASMF: the type of variation depends on the type of individual changes introduced in the updated version.

- *If condition 5 of Annex III of Regulation 1234/2008 applies (all variations in the group are changes that concern the ASMF), the update can be submitted as a grouped application according to the highest type of the individual changes.*
- *In case of substantial changes, it is recommended to submit a single type II variation under category B.I.z).*

Publication Manager

S. RAKOTOMANGA, Pharm D
s.rakotomanga@medibridge.fr
Energy 4 - 34 av. de l'Europe - BP 136 - 78148 Vélizy Cedex
tél +33 (0)1 39 45 60 00 - fax +33 (0)1 39 46 36 60
www.medibridge.fr