COMMENTS relative to PUBLIC CONSULTATION PAPER
REVIEW OF THE VARIATIONS GUIDELINES
A - Administrative Changes
B -Quality Changes

The SFSTP Commission untitled « Nouvelle réglementation Européenne Variations (1234/2008) : Problématique de la gestion des changements» (New European Variations Regulation (1234/2008): Problematic of Change Control) is a French Working Group that aims at elaborating a practical guide for the implementation of the New European Variations Regulation for CMC Departments.

The comments of this SFSTP Commission for the purpose of the public consultation on Part A – Administrative Changes and Part B – Quality Changes of the review of variations guidelines are listed hereafter with reference to the corresponding variation.

Generally speaking, the Commission points out that only some of the variations classified by the CMDh and CMDv via the "Article 5 Procedure" have been included in the proposed update. And such a fact needs to be clarified and/or commented.

A. ADMINITRATIVE CHANGES

A.3 Change in name of the active substance or of an excipient	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
	1, 2	**1, 2**	**IA_{IN}**
Conditions			
1. The active substance/excipient shall remain the same.			
Documentation			
1. Proof of acceptance by WHO or copy of the INN list. If applicable, proof that the change is in line with the Ph. Eur. For herbal medicinal product, declaration that the name is in accordance with the Note for Guidance on Quality of Herbal Medicinal Products, and with the guideline on declaration of herbal substances and herbal preparations in (traditional) herbal medicinal products.			

Comments on change description, condition and documentation:

This tends to increase the administrative load and the number of variations to submit (with excipient), whereas the variations regulation (regulation 1234/2008) "aims to establish a simple, and more flexible legal framework".

This tends to submit variations relative to Ph. Eur. update, whereas the information on variations regulation (regulation 1234/2008) states that "There is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that compliance with the updated monograph is implemented within six months of its publication and reference is made to the 'current edition' in the dossier of an authorised medicinal product".

A.4 Change in the name and/or address of a manufacturer (including where relevant quality control testing sites), ASMF holder, 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 or a manufacturer of a novel excipient.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
	1	1, 2, 3	IA

Comments on change:

This tends to increase the administrative load and the number of variations to submit (with ASMF holder), whereas the variations regulation (regulation 1234/2008) "aims to establish a simple, … and more flexible legal framework"

A.5 Change in the name and/or address of a manufacturer of the finished product, including importer, batch release or quality control testing sites	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Manufacturer responsible for one or several activities including batch release	1	1, 2	IA_{IN}
b) All other (including supplier of packaging components or devices (where specified in the product dossier))	1	2	IA

Comments on change

This tends to increase the administrative load and the number of variations to submit (with importer), whereas the variations regulation (regulation 1234/2008) "aims to establish a simple, … and more flexible legal framework".

B. QUALITY CHANGES

B.I. ACTIVE SUBSTANCE

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 supplied	Procedure type
j) Changes to quality control testing arrangements for a biological active substance-replacement or addition of a site where batch control/testing including a biological/immunological / immunochemical methods takes place			II

Comments on change and type II:

This tends to go back to the previous system with the use of type II by default concerning biologicals.

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 supplied	Procedure type
c) Deletion of a non-significant in-process test	1, 2, 7	1, 2, 5	IA
Conditions			
7 The specification parameter does not concern a critical parameter for example any of the following: 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, any request for skip testing.			

Comment to change, condition and type IA:

This deletion of a non-significant test as a type IA variation was introduced in variations regulation (regulation 1234/2008).
This restrictive condition with all examples tends to let this change useless as type IA.
In addition, examples of non-significant in process-test could be provided.

B.I.b.1 Change in the specification parameters and/or limits of an active substance, starting material/ intermediate/ reagent used in the manufacturing process of the active substance	Conditions to be fulfilled	Documentation to be supplied	Procedure type
c) Addition of a new specification parameter to the specification with its corresponding test method	1, 2, 5, 6, 7	1, 2, 3, 4, 5, 7	IA
Documentation			
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 specification. For herbal medicinal products, comparative disintegration data may be acceptable.			

Comments on documentation:

The reason why the comparative dissolution profile data may be appropriate, while simply adding a new specification parameter to the specification for an active substance, starting material or intermediate, is quite unclear and need to be clarified.

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 supplied	Procedure type
d) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter e.g. odour)	1, 2, 8	1, 2, 6	IA
Conditions			
8 The specification parameter does not concern a critical parameter, for example any of the following: 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, any request for skip testing.			

Comments on condition and type IA:

This deletion of non-significant test in type IA was introduced in variations regulation (regulation 1234/2008).
This restrictive condition with all examples tends to let this change useless as type IA.

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.	Conditions to be fulfilled	Documentation to be supplied	Procedure type
c) Change to an approved stability protocol	1, 2	1, 4	IA

Comments on change:

This tends to increase the administrative load and the number of variations to submit (with stability protocol), whereas the variations regulation (regulation 1234/2008) "aims to establish a simple, … and more flexible legal framework".

B.II. FINISHED PRODUCT

B.II.a.3 Changes in the composition (excipients) of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure 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
Conditions			
11 For veterinary medicinal products for oral use, the change does not affect the uptake by target animal species.			

Comments on change condition:

Information on the uptake by target animal species is not part of all veterinary medicinal products dossiers. The mention "When described in the dossier" could be added to the change.

B.II.a.3 Changes in the composition (excipients) of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Changes in components of the flavouring or colouring system			
3. Veterinary medicinal products for oral use for which the colouring or flavouring agent is important for the uptake by target animal species			II

Comments on type II classification:

This tends to go back to the previous system with the use of type II by default, here concerning all veterinary medicinal products (biologicals or not).

B.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Replacement or addition of a site where batch control/testing takes place	2, 3, 4, 5	1, 2, 5	IA
b) Replacement or addition of a site where batch control/testing takes place for a biological/immunological product and one of the test methods performed at that site is a biological / immunological / immunochemical method			II
c) Replacement or addition of a manufacturer responsible for importation and/or batch release			
1. Not including batch control/testing	1, 2, 5	1, 2, 3, 4, 5	IA_{IN}
2. Including batch control/testing.	1, 2, 3, 4, 5		II

Comments on change:

This tends to increase the administrative load and the number of variations to submit (with importer), whereas the variations regulation (regulation 1234/2008) “aims to establish a simple, … and more flexible legal framework”.
Moreover, the Importer concept is not mentioned in module 3.

B.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
b) Replacement or addition of a site where batch control/testing takes place for a biological/immunological product and one of the test methods performed at that site is a biological / immunological / immunochemical method			II

Comments on change and type II:

This tends to go back to the previous system with the use of type II by default concerning biologicals.

B.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
c) Replacement or addition of a manufacturer responsible for importation and/or batch release			
2. Including batch control/testing.	1, 2, 3, 4, 5		II

Comment to change and type II:

This variation with the associated conditions should be an IA_{IN} (see the current classification guideline).

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 supplied	Procedure type
z) Change in the manufacturing process of the finished product: minor change in the manufacturing process of modified release oral dosage form.			IB
z) Change in the manufacturing process of the finished product: minor change in the manufacturing process of solution for injection/infusion.			IB
z) Minor change in the manufacturing process of the finished product-Change in the holding time of an intermediate.			IB
z) Change in the packaging material of bulk product not in contact with the bulk product formulation (including replacement or addition).	*		IA
z) Minor change in the manufacturing process of a sterile finished product after the primary packaging step.			IB
Conditions			
* The secondary packaging does not play a functional role on the stability of the bulk product, or if it does, it is not less protective than the approved one.			

Comments on change

The reasons why the five variations classified as Variations B.II.b.3.z via the "Article 5 procedure" have not been included in this classification update need to be clarified.

B.II.b.4 Change in the batch size (including batch size ranges) of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
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

Comments on change

The criteria or conditions leading to the requirement of a new bioequivalence study while changing batch size are not specified and need to be clarified.

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 supplied	Procedure type
c) Deletion of a non-significant in-process test	1, 2, 7	1, 2, 6	IA
Conditions			
7 The in-process test does not concern the control of a critical parameter, for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the excipient), any critical physical characteristics e.g. 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 dosage form.			

Comment to change, condition and type IA:

This deletion of non-significant test in type IA was introduced in variations regulation (regulation 1234/2008).
This restrictive condition with all examples tends to let this change useless as type IA.
In addition, examples of non-significant in process-test could be provided.

B.II.c.1 Change in the specification parameters and/or limits of an excipient	Conditions to be fulfilled	Documentation to be supplied	Procedure type
c) Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	1, 2, 8	1, 2, 7	IA
Conditions			
8 The specification parameter does not concern a critical parameter for example any of the following: impurities (unless a particular solvent is definitely not used in the manufacture of the excipient), any critical physical characteristics e.g. 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 dosage form.			

Comments on change, condition and type IA:

This deletion of non-significant test in type IA was introduced in variations regulation (regulation 1234/2008).
This restrictive condition with all examples tends to let this change useless as type IA.
In addition, examples of non-significant in process-test could be provided.

B.II.d.1 Change in the specification parameters and/or limits of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
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
Conditions			
9. The specification parameter or proposal for the specific dosage form does not concern a critical parameter for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the finished product), physical characteristics (e.g. hardness or friability for uncoated tablets), dimensions, a test that is required for the for the particular dosage form in accordance with the general notices of the Ph. Eur., any request for skip testing.			

Comments on change, condition and type IA:

This deletion of non-significant test in type IA was introduced in variations regulation (regulation 1234/2008).
This restrictive condition with all examples (including dimensions) tends to let this change useless as type IA.

B.II.d.1 Change in the specification parameters and/or limits of the finished product		Conditions to be fulfilled	Documentation to be supplied	Procedure type
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}**
Conditions				
8.	If 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 totally in line with the pre January 2008 (non harmonised) situation and does not include any additional specified controls over and above the Pharmacopoeia requirements for the particular dosage form and the proposed controls are totally in line with the harmonised monograph.			

Comments on change and condition:

This tends to submit variations relative to Ph. Eur. update, whereas the information on variations regulation (regulation 1234/2008) states that "There is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that compliance with the updated monograph is implemented within six months of its publication and reference is made to the 'current edition' in the dossier of an authorised medicinal product".

B.II.d.1 Change in the specification parameters and/or limits of the finished product		Conditions to be fulfilled	Documentation to be supplied	Procedure type
z)	**Ph. Eur. 2.9.40 Uniformity of Dosage Units is introduced to replace the current method Ph. Eur. 2.9.6 Uniformity of Content.** **Parallèle avec la nouvelle variation i**			**IB**
z)	**Ph. Eur. 2.9.40 Uniformity of dosage units (by mass variation) is introduced to replace the current method Ph. Eur. 2.9.5 Uniformity of mass.** **Please note that new specification (test and limits) should be introduced** **Parallèle avec la nouvelle variation i**			**IB**
z)	**Change in the microbiological purity specification parameters of the finished product to comply with Ph.Eur. A change to the finished products specifications in order to comply with Ph. Eur. could also possibly be acceptable as a Type IA notification in certain circumstances, taking into account the general acceptance that the new limits are acceptable for the specific dosage forms. It is up to the Applicant to provide all necessary data for the justification of the classification.** **Parallèle avec la nouvelle variation h**			**IB** **(IA)**
z)	**Reduction in the testing frequency of an analysis, from routine testing to skip or periodic testing (microbial testing of finished product).**			**IB**
z)	**Change in the specification parameters and/or limits of the finished product to more accurately describe the appearance of the drug product.**	*		**IA**
Conditions				
*	**The change is not a result of any unexpected events arising during manufacture or testing of the drug product.**			

Comments on change

Why only some above mentioned variations classified via Article 5 procedure, as variation B.II.d.1.z have been included in this update (as variations B.II.d.1.h, & B.II.d.1.i)?

B.II.d.2 Change in test procedure for the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
e) Update of the test procedure to comply with the updated general monograph in the Ph. Eur.	**2, 3, 4, 5**	**1**	**IA**
Conditions			
2. There have been no changes of the total impurity limits; no new unqualified impurities are detected			
3. The method of analysis should remain the same (e.g. a change in column length or temperature, but not a different type of column or method);			
4. The test method is not a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).			
5. The registered test procedure already refers to the general monograph of the Ph. Eur and any changes are minor in nature and require updating of the dossier information.			
Documentation			
1. Amendment of the relevant section(s) of the dossier (presented in the EU-CTD format or NTA volume 6B format for veterinary products, as appropriate), including a description of the analytical methodology, a summary of validation data, revised specifications for impurities (if applicable).			

Comments on change and conditions:

This tends to submit variations relative to Ph. Eur. update, whereas the information on variations regulation (regulation 1234/2008) states that “There is no need to notify the competent authorities of an updated monograph of the European pharmacopoeia or a national pharmacopoeia of a Member State in the case that compliance with the updated monograph is implemented within six months of its publication and reference is made to the 'current edition' in the dossier of an authorised medicinal product”.

B.II.f.1 Change in the shelf-life or storage conditions of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
e) Change to an approved stability protocol	**1, 2**	**1, 4**	**IA**

Comments on change:

This tends to increase the administrative load and the number of variations to submit (with stability protocol), whereas the variations regulation (regulation 1234/2008) “aims to establish a simple, … and more flexible legal framework”, especially as such a variation can not occur alone.

B.III CEP/TSE/MONOGRAPHS

B.III.2 Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State	**Conditions to be fulfilled**	**Documentation to be supplied**	**Procedure type**
a) Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State			
1. Active substance	**1, 2, 3, 4, 5**	**1, 2, 3, 4, 5**	**IA_{IN}**
2. Excipient/active substance starting material	**1, 2,4**	**1, 2, 3, 4, 5**	**IA**
b) Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	**1, 2, 4, 5**	**1, 2, 3, 4, 5**	**IA**
c) Change in specifications from a national pharmacopoeia of a Member State to the Ph. Eur.	**1, 4, 5**	**1, 2, 3, 4, 5**	**IA**
Documentation			
3. Batch analysis data (in a comparative tabulated format) on two production batches of the relevant substance for all tests in the new specification and additionally, where appropriate, comparative dissolution profile data for the finished product on at least one pilot batch. For herbal medicinal products, comparative disintegration data may be acceptable.			

Comments on documentation:

The cases where comparative dissolution profile data may be appropriate, need to be clarified.