12.07.2012

Submission of comments on 'Guideline on the Details of the Various Categories of Variations' (Sanco.ddg1.d.5(2012)817838)

Comments from:

Name of organisation or individual
European Federation of Pharmaceutical Industries and Associations (EFPIA) **European Biopharmaceutical Enterprises (EBE)** **European Vaccine Manufacturers (EVM)**

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	EFPIA appreciates the opportunity to comment on this revised Variation Classification guideline. Whilst we believe that a number of the proposed changes are positive and moving the document in the right direction, we have concerns with several of the proposed changes, as well as on the existing text.
	One of the major objectives of the Better Regulation initiative, as described in the Commission Public Consultation Paper (October 2007) was to adapt to the new ICH quality concepts outlined in ICH Q8 (R2)/Q11, Q9 and Q10 *e.g. 'by providing further flexibility to manufacturers who have undertaken the efforts to put in place modern quality tools'.* Whilst we welcome a number of the proposed changes in this current revision, which are intended to accommodate and align with key elements of these quality tools, we believe that these elements need to be more fully integrated into the body of the guideline, because as currently written, they seem to have been introduced as add-ons to the existing text. Overall, we would assert that greater efforts could have been made to introduce more substantial changes to facilitate a *'more science and risk based approach'* for reviewing post approval changes, where a MAH has applied an advanced QbD approach to product development, applies quality risk management principles and has implemented a robust Pharmaceutical Quality System. This would make a significant contribution to creating a more enabling regulatory environment in the EU, which would facilitate and foster continual improvement and innovation in pharmaceutical manufacturing.
	We believe that the sections dealing with changes to analytical methods are overly stringent. Opportunities to introduce more flexibility, by accommodating a more science and risk based approach to assessing the impact of changes to analytical methods should be considered. In line with quality risk management principles (as defined in Q9) the variation categorisation for changes to an analytical method should be commensurate with the risk associated with the change. To assess the risks associated with changes in analytical methods a range of factors should be considered, including: • The maturity and associated knowledge of the analytical technique; • The general capability of the analytical technique; • The criticality of the quality attribute being analysed; • The criticality of the material being analysed; • The capability of the company's Pharmaceutical Quality System to manage changes. By taking into account the above factors, we believe there are opportunities to introduce more flexibility in order to facilitate changes to analytical methods, with a more appropriate level of regulatory oversight.

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	Addressing the risks associated with the maturity and knowledge of the analytical technique and linking the change control categorisation more closely with the general chapters in the European Pharmacopoeia is one approach that should be considered at this time.
	We welcome the separation of 'Design Space' and 'Post-approval Change Management Protocol' variation categories. We also welcome the elaboration of the sections dealing with 'Post-approval Change Management Protocols' (PACM Protocols). However, we believe more flexibility could be introduced, by relaxing some of the conditions for the PACM Protocol changes, which would encourage their use.
	EFPIA also propose that the guideline raises the possibility for accelerated assessment of variations arising from unforeseen circumstances and where the supply of an essential medicine might be disrupted following standard timelines. The timeframes for such assessments do not need detailing as these should be set on a case by case basis, following standard variation procedures.
	We believe it would be valuable to reconsider the classification for a number of variation categories relating to biological/immunological products and substances (i.e. either by removing the current excluding condition(s), or by downgrading the classification from a type II to a type IB or IA). In a number of instances there is strong scientific evidence that the changes have no impact on the Quality, Safety or Efficacy of the product, and therefore a comprehensive type II assessment process (as currently foreseen) appears disproportionate to the potential risks (obvious examples include minor changes to manufacturing steps/equipment for finished products, minor changes to analytical methods, etc.). In this context, it would be helpful if the supportive documentation to be supplied could be defined more precisely for type II variations - in particular concerning required stability data for biologics. Moreover, common changes to CTD Appendix A.1 (Facilities and Equipment) should be addressed in the classification guideline, e.g. an update of floor plans, minor reconstructions, minor changes in cleaning procedures etc., with a difference in the assessment being made between product-contact equipment and non-product-contact changes (where concepts are not touched).
	Most member companies have experienced inconsistent interpretation/application of the Classification guideline by individual Member States who have already implemented the Variation Regulation at national level. We would recommend that Q&A documents are developed by the EMA and/or the CMD(h-v) to provide harmonised interpretations when divergent views are recorded. We also recommend that processes be put in place allowing (1) industry to notify examples of such situations resulting from divergent interpretations and (2) the collaborative development of common understanding across agencies as well as between industry and authorities.

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	We have noted that there are a number of instances where terminology is used inconsistently or inappropriately throughout the document, and this can be classified as follows: 1. The revision of the guideline introduced a number of new terms / expressions that would require a definition to avoid divergent interpretations. Examples of such expressions are: • "complex process" in variation B.II.b.1.c • "novel excipients" in A4 and others If a definition cannot easily be developed the provision of examples would certainly help. 2. Inconsistency with existing ICH quality guidelines: Whilst the document introduces a number of QbD related terms, these are not used consistently or appropriately across the document; e.g. the terms 'specification parameter', 'parameter', 'material attributes', 'critical physical characteristics' , 'acceptance criteria in the parameters tested' are used throughout the document, and do not appear to be aligned with Q8 (R2) terminology. Furthermore the terms 'acknowledged enhanced development approach' and 'enhanced development approach' are used throughout the guideline. These terms are not consistent with Q8 (R2). The term 'already approved monitoring scheme' is used, and it is unclear what this term is referring to. 3. In other instances, the guideline lacks consistency using different expressions for the same notion. It is best exemplified in the case of "substantial change" as used in variation B.I.a.2.b for instance. We understand that "substantial" is used here to mean the same as "major". We believe that it would be clearer to consistently use the term "major" and/or "major variation" throughout the guideline, as this term is clearly defined in the Regulation. We recommend a terminology consistency check across the guideline. In order to avoid confusion it is essential that these issues around terminology are addressed before the Classification guideline is finalised.
	We would like to reiterate the concerns repeatedly expressed regarding the need to improve the user-friendliness of the guideline. The whole structure of the document may need to be revised in the future. – The current structure and numbering system of the guideline is to a certain extent causing confusion, and a structure referring to the CTD-Q sections would be much more user-friendly. As a short-term improvement, we suggest to already introduce references to the CTD-Q sections numbering system in the supporting data / documentation sections in this revised version of the guideline.

Stakeholder number *(To be completed by the Agency)*	General comment (if any)
	Also, the classification for a given change is not always obvious at first read and this may be confusing. For example, for several variations categories it is only when reading the list of conditions till the very end that the reader may notice that one of the conditions excludes his particular change from a Type IA (or IB) category (e.g. "the product is not a biological/immunological product"). Decision trees may be introduced for the more complex variations categories.
	In section 1.1 of the consultation paper it is mentioned that "*this contribution takes into account the recommendations delivered in accordance with Article 5 of the Variations Regulation since the entry into force of guidelines on the details of the various categories of variations in January 2010"*. However we notice that some of the changes included in the current version of the CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008 have not been integrated in the proposed revision of the classification guideline. We would like to recommend integrating these recommendations along with the background elements and conditions necessary for an easy use, in case where no obvious categories of variations would fit.
	EFPIA would also recommend that there is an open dialogue with the Commission and other stakeholders on the revision to this guidance. This would be greatly facilitated by a workshop lead by the Commission to discuss major comments in further detail.
	These general/strategic comments are further supported by the detailed comments provided hereafter.

2. Specific comments on text

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
A. ADMINISTRATIVE CHANGES			
A.3		**Comment:** The proposed addition under Documentation item 1 "*If applicable, proof that the change is in line with the Ph.Eur.*" should be better defined. **Proposed change:** Amend Documentation item 1: *If applicable, proof that the change* ***complies*** ~~*is in line*~~ *with the Ph.Eur* **or another internationally well-accepted references**.	e
A.4		**Comment:** It is not clear what a 'novel excipient 'is in this context. Is this an excipient without a pharmacopoeial monograph? The main text states ***"...****where no Ph.Eur. Certificate of Suitability is part of the approved dossier or a manufacturer of a novel excipient"*. This sentence requires clarification as it may be confusing for the reader who may wonder what to do in case of a change where a Ph.Eur. Certificate of Suitability was part of the approved dossier, or in case of a change relating to a manufacturer of a novel excipient. We propose to add a note with references to variation B.III.A and variation B.II.C.5. In the context of the work undertaken by the Working Group on Active Substance Master File, reflection on the possibility to limit the information on ASMF holder included in the MA dossier (i.e. reference to ASMF number). **Proposed change:** Revise the title of the variation ....*of the active substance (where specified in the product dossier)..... or a manufacturer of a*	m

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		novel excipient **where no pharmacopoeial monograph is available**. Please add a note: **Refer to variation B.III.1in case of a change where a Ph. Eur. Certificate of Suitability was part of the approved dossier** **Refer to variation B.II.c.5 in case of change in manufacturer of a novel excipient**	
A.5		**Comment:** In variation A.5 a) the notion of "*one or several activities*" does not clearly define which manufacturing activities are concerned by a type IA IN variation in case of change in the name/address of the manufacturer. The same remark applies to variation A.5 b) since its scope depends on the scope of a) ("*all other*" activities, handled through a type IA variation). We think that variation A.5 a) should concern only changes in the name/address of sites where core manufacturing activities takes place, including batch release but also packaging, importation and quality control testing. In addition, the addition of supplier of packaging components or device under variation A.5 b) does not seem to be related to the overall scope of the variation A.5 which only applies to finished product manufacturer. Condition 1 requires clarification or rephrasing. The definition of 'importer' needs to be clarified in a note. We suggest a revised wording for condition 1 for clarity purpose. **Proposed change:** Revise description of variation A.5 a) *a) Manufacturer responsible for one or several* ***core*** *activities including* **packaging, importation, quality control testing and** *batch release* Revise condition 1	C

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		All manufacturing operations shall remain the same for the specific site undergoing the name and/or address change	
A.7		**Comment:** In the proposed text, variation A.7 a) relates either to the active substance manufacturers or to the finished product ones, while variation A.7 b) only applies to these latter. In order to better clarify the field of application of the variation, the following amendment is proposed: • Variation A.7 a) should only apply to the deletion of an active substance manufacturer; for this variation, the Condition 3 should be deleted. • Variation A.7 b should apply to the deletion of a finished product manufacturer), in turn divided in a case 1 (site located in EU/EEA) and in a case 2 (site located outside the EU/EEA). For both cases, the Condition 3 should be applied.	M
A.7		**Comment:** Variation A.7. b) relates to the deletion of manufacturing sites "*for finished product or intermediate of the finished product, […], when the site in question is outside the EU/EEA, no GMP mutual recognition agreement (MRA) exists with the country in question and notice has been given by the authorities of the intention to perform an inspection of this site*." The rationale behind the notion of 'notice by the authority of the intention to perform an inspection of the concerned site should be clarified.	m
A.7 b)		**Comment:** There is a need to clarify that the 3 items have to be fulfilled concomitantly to lead to submission of this variation as a type IA_{IN}. **Proposed change:** *b) for finished product or intermediate of the finished product, including packaging sites, when the site in question is outside the EU/EEA,* **and** *no GMP mutual recognition agreement (MRA) exists with the country in question and notice has been given by the authorities of the intention to perform an inspection of this site.*	m
A.7 Condition		**Comment:** We assume that Condition 3 is not relevant if RTR Testing is in place; i.e. no testing, therefore no	m

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
3		testing site in the EU. Clarification is needed.	
A.7 (B.1.a.1) (B.II.b.1)		**Comment:** Documentation – The application form referred to in is the new MA application form and not the current variation application form. This information is generally forgotten once the MA has been authorised and the contact details become subject to Manufacturing Authorisation maintained by the Competent Authority Inspectorate. There is little value in maintaining this part of the New MA application form as well as module 3.2.P.3.1. A flow chart/schematic illustrating supply chain and site interaction with the product is also required at time of initial MA application. It would be valuable to maintain this document and therefore add it as a document requirement. Documentation 1. Clear Present versus Proposed in the variation application form 2. Updated dossier modules Revised schematic of product flow between sites	m

Variations reference	Stakeholder number ***(To be completed by the Agency)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
B. QUALITY CHANGES			
B.I.a.1.d		Subclass B.I.a.1.d) relates to the introduction of a 'new manufacturer of material for which an assessment is required of viral safety and/or SE risk and is indicated as a type II variation'. **Comment:** - This subclass should be split into 2 cases: When the change does not require an evaluation of the viral safety or BSE risk and if the specifications are unchanged, this should be a type IA. In other cases, it should be a type IB. - 'Material' should be defined. If this covers the starting materials, reagents and intermediates please clarify the wording. **<u>Proposed change</u>:** New manufacturer of material ~~for which an assessment is required of viral safety and/or TSE risk: type II~~ i) for which an assessment is required of viral safety and/or TSE risk: type IB. ii) for which no assessment of viral safety and/or TSE risk is required: type IA. (add condition 6) Conditions: […] Add condition 6: Specifications are unchanged.	M e
B.I.a.1.e		**Comment:** A Type II variation for a manufacturer of a non-biological starting material or reagent does not seem necessary. This subclass should be split into several categories. **<u>Proposed change</u>:** The change relates to: ~~a biological active substance or a starting material / reagent / intermediate used in the manufacture of a biological/immunological Product~~	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		- an active substance / intermediate used in the manufacture of biological product : Type II **- a starting material or a reagent:** ***of biological origin (with or without change in the specifications): Type II** ***non biological with no change in the specifications: Type IB**	
B.I.a.1.g		**Comment:** There is a need to clarify "*significant update*" in the context of the wording. We understand it to mean "*major update*".	e
B.I.a.1.i		**Comment:** We recommend to include the word "milling" as well as "micronisation", as these are technically different processes. **<u>Proposed change</u>:** Introduction of a new site of micronisation <u>or milling</u> **Comment:** The Documentation 8 states: "Proof that the proposed site is appropriately authorised for the **pharmaceutical form** or **product** or manufacturing operation concerned, i.e.,..." Since the variation is aimed to introduce a micronisation site for the active substance, the text in **bold** seems redundant. **<u>Proposed change</u>:** The text should be amended as follow: "Proof that the proposed site is appropriately authorised for the ~~pharmaceutical form or product or~~ manufacturing operation concerned, i.e.,..."	m e
B.I.a.1.j		**Comment:** With the addition of B.I.A.1.j Changes to quality control testing arrangements for a biological active-substance-replacement or addition of a site where batch control/testing including a	C

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		biological/immunological/immunochemical method takes place is now proposed as a Type II variation. We recommend not to add B.I.A.1.j. A Type II for this type of variation is too stringent and seems disproportionate. At the very least, if comparability of testing results between sites has been adequately demonstrated type IB would be adequate. It is unclear what data would be needed to support this Type II variation as method transfer documents are generally considered GMP information subject to inspection and could still be submitted, if required, as part a Type IB variation. In case of specific concerns upgrade is possible through the CA. **Proposed change:** Delete B.I.a.1.j and go back to type IB by default	
B.I.a.1.k		**Comment:** Update of storage site for Cell Banks is not expected to affect quality of product and should be handled as administrative change and submitted accordingly to the competent authorities. It is reflected in the documentation 1 and 5. **Proposed change:** New storage site of Master Cell Bank and/or Working Cell Banks (if specified in the dossier). Suggested Procedure type IA rather than IB.	M
B.I.a.2.c		**Comment:** The way the newly added text *("…, which may have a significant impact on the quality, safety and efficacy…"*) has been incorporated makes the reading of the sub-category rather complex. It would also add clarity if the guidance would specify that by "protocol" it refers to "post-approval change management protocol" (as newly introduced in category B.I.f). **Proposed change:** For clarity we propose the following rewording: The change may have a significant impact on quality, safety and efficacy of the medicinal product and is not covered by a post-approval change management protocol (foreseen in category B.I.f.1	e

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		to 4) and refers to o a biological/immunological substance or use of a different chemically derived substance in the manufacture of a biological/immunological substance	
B.I.a.2.f (also B.I.a.4.g)		**Comment:** Obligation of reporting non-critical parameters will in itself give an unnecessary burden on industry and regulators. It will furthermore make application of enhanced approach highly unattractive. Furthermore, as many parts of the world still do not accept the EU Type IA Annual Reporting system, a Type IA annual reporting of a minor change with no negative impact on quality and no significant impact on safety and efficacy will cause huge amount of industrial internal logistic and other resources inappropriate for a worldwide fast implementation. For example, a minor change in stirring of a propeller (time or speed) for an active substance with unchanged non critical parameter (before and after) should be handled as a GMP issue and not with a Type IA Annual Reporting causing delayed worldwide implementation and disproportionate logistic efforts. This is in line with the EMA guidance Doc. Ref. EMEA/INS/GMP/2270 **Proposed change:** We feel that this classification is not needed in B.1.a.2 because the need to notify is already covered by B.I.e. and B.I.f.	C
B.I.a.2 B.I.a.4 B.II.b.3 B.II.b.5 Conditions 8 and 9 for all		**Comment:** Use of the terms like "an acknowledged enhanced development" and "approved monitoring scheme" are unclear in the context of these conditions. To avoid confusion EFPIA recommends using ICH Q8-Q10 terminology. Further consideration of accommodating key elements of ICH Q8, Q9 and Q10 implementation: we recommend that text is included in the guideline to clearly indicate that movement within a Design Space does not constitute a change that requires a variation to be submitted. Furthermore, the inclusion of more granularity in the Design Space classifications would be helpful.	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
B.I.a.4		**Comment:** The clarity of condition 7 could be improved by itemizing the given examples in a separate sentence. In addition the term "assay" should be made more precise. **<u>Proposed change</u>:** reformulate condition 7 as follows: The specification parameter does not concern a critical parameter. Examples of critical parameters include potency assay, ...	e
B.I.a.4.c		**Comment:** This variation should also be applicable to the deletion of a non-significant in-process limit **<u>Proposed change</u>:** Deletion of a non-significant in-process test **and/or limits**	m
B.I.a.4.g		**<u>Proposed change</u>:** We feel that this category is already covered by B.I.e. and B.I.f. and therefore should be deleted (See comments above for B.I.a.2.f)	C
B.I.b.1		**Comment:** The current presentation of this variation mixes changes relating to specification limits and changes to specification parameters **<u>Proposed change</u>:** Regroup subcase h) with subcases c), d) and e). Place subcases f) and g) at the end of the list	e

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
B.I.b.1.c		**Comment:** Documentation number 5 has been added as a requirement for this change when a new specification parameter is added to the active substance. Number 5 in the documentation list is to provide comparative dissolution profile for the finished product on at least one pilot batch containing the active substance complying with the current and proposed specification? This does not appear to be appropriate when just adding specification to the active substance. It would be consistent to add to the wording of this variation "or replacement" to be consistent with variation B.I.b.1.h) which is to be used in case of safety or quality issues, but there are many cases where there is no such issue. Adding replacement, also means that the word new needs to be removed. **Proposed change:** Do not add documentation item 5 to B.I.b.1.c. (c) Addition or replacement of a ~~new~~ specification parameter to the specification with its corresponding test method.	e
B.I.b.1.d		**Comment:** There is no need to add condition 8, as B.I.b.1 d already refers to non-significant specification parameters. It is not common to add examples, so delete odour. It may lead to a wrong interpretation of non-significant. This variation should also be applicable to the deletion of a non-significant specification limit. **Proposed change:** d) Deletion of a non-significant specification parameter **and/or limit** (e.g. deletion of an obsolete parameter ~~e.g. odour~~ Conditions: 1, 2, ~~8~~ ~~Condition 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~~	m

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		~~manufacture of the active substance), any critical physical characteristics e.g. particle size, bulk of tapped density, identity test, water, any request for skip testing.~~	
B.I.b.1.f		**Comment:** The text should specify that a Type II procedure should only apply when the change is expected to have a significant impact on the overall quality of the active substance and/or the finished product. It is suggested to add a condition 9, applicable to category B.I.b.1.h and g. Align wording by adding into "which may have a significant effect on the overall quality of the active substance and/or the finished product" into the (f) sub-category. **Proposed change:** Add a new condition 9, see below.	m
B.I.b.1.g		**Comment:** The end of the sentence "which may have a significant effect on the overall quality of the active substance and/or the finished product" should be moved into the Conditions column. **Proposed change:** 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~~**.** **- if condition 9 is met: Type IB** **- if condition 9 is not met: Type II** Conditions: […] 9. The change outside approved specification limit rang for the active substance or widening of specifications limits for starting materials / intermediates has no significant effect on the overall quality of the active substance and/or the finished product.	m
B.I.b.1. h, i		**Comment:** It is proposed to delete documentation item 5 also for categories h and i in its whole.	

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		Proposed change: Documentation 5 ~~Where appropriate, comparative dissolution profile data for the finished product on at least one pilot bath containing the active substance complying with the current and proposed specification. For herbal medicinal products, comparative disintegration data may be acceptable.~~	
B.I.b.1.h		**Comment:** The text reads "Addition or replacement (excluding biological or immunological substance) of a specification parameter with its corresponding test method as a result of a safety or quality issue". Due to the exclusion into brackets, it is not possible for manufacturers of biological or immunological substances to refer to this sub-category. However, when reading the whole text of category B.I.b.1 (including the conditions), the normal conclusion for the reader is that in the case of such a change for a biological or immunological substance the classification should be IB by default. Since it is a Type IB anyhow, the following change is proposed. **Proposed change:** Remove the parenthesis "…*~~(excluding biological or immunological substance)~~…*"	e
B.I.b.1.i		**Comment:** To clarify what is meant by "non-official pharmacopoeia"? Would it be possible to get a list of concerned countries? Official Pharmacopoeia (in order of preference): PhEur, Member State Pharmacopoeia e.g. BP, FrP etc, USP/USP-NF, JP. Standard practice is EU and ICH regions. In cases where in-house specifications for the active substance comply to a non official Pharmacopoeia or a Pharmacopoeia of a third country the variation should be a type IA. **Proposed change:** B.I.b.1.i) Where there is no monograph in the European Pharmacopoeia or the national pharmacopoeia of a Member State for the active substance, a change in specification from in-	m

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		house to a non official Pharmacopoeia or a Pharmacopoeia of a third country**:** **- in-house specifications for the active substance comply to the non official Pharmacopoeia or a Pharmacopoeia of a third country: type IA –** Documentation: **Justification that in-house specifications comply to the official Pharmacopoeia.** **- if not:** type IB	
B.I.b.2		**Comment:** An additional subclass is needed to address cases of addition of a biological / immunological / immunochemical test procedure for a biological substance with no other changes to the test methods or to the specifications of the active substance. **Proposed change:** f) Addition of a biological / immunological / immunochemical test method for a biological substance with no other changes to the test methods or to the specifications and no consequences on the quality of the substance: type IB.	
B.I.b.2.a		B.I.b.2 .a) Minor changes to an approved test procedure – Type IA. **Comment:** Since minor changes to physico-chemical tests are classified as type IA variations validation reports should not be submitted for assessment, especially if there is no need to update the corresponding CTD section. **Proposed change:** Documentation 1: […]. **Validation reports should be available for inspection at the manufacturer site but should not be submitted in the variation application of minor changes to physico-chemical tests**.	M
B.I.b.2c		**Comment:** If no significant effect, no need to exclude biologicals. **Proposed change:** c), condition 6: we suggest removing this specific condition for biologics in case these are minor	e

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		updates for continuous improvement of the process according to ICH Q10 (for changes that have a more administrative character and have no anticipated impact on Quality, Safety, Efficacy).	
B.I.b.2.d		**Comment:** The added word to B.I.b.2.d "substantial" to this category suggests that non-substantial, i.e. minor changes to biological/immunological/immunochemical test methods or a method using a biological reagent for a biological active substance can be filed as a Type IA or Type IB. **Proposed change:** f) Minor changes to biological/immunological/immunochemical test methods or a method using a biological reagent for a biological active substance. Conditions to be fulfilled: 1, 2, 3, 5 Documentation to be supplied: 1, 2 Procedure type: IB	e
B.I.b.2.d		**Comment:** The meaning of "substantial" should be clarified and better defined. Define 'minor' change? (how could we deal with a "minor change" that has required an "appropriate validation" (condition '1') **Proposed change:** Replace substantial change by major change, in line with the designation of a Type II variation, which is a major change.	M
B.I.b.2e		**Comment:** Split variation B.I.b.2.e) into two categories, one for intermediate and starting materials and one for active substance. Other changes to a test procedure for starting material/intermediate to be filed as Type IA and other changes to a test procedure for the active substance to be filed as type IB. **Proposed change:** ad (e, other changes to a test procedure): we suggest downgrading to type IA for a starting material or intermediate.	m

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
B.I.b.2.f		**Comment:** In order to improve clarity, a distinction between adjustments and changes would be beneficial. Adjustment ranges are either defined in Ph.Eur. Chapter 2.2.46 for chromatographic methods, or must be registered and covered by validation data. **Proposed Change:** Introduce the following variation sub-category, with new condition: **f) Adjustments as allowed by the compendia or within registered and validated ranges** **Condition 8: (see below)** **Variation Type IA**	
B.I.b.2.g		**Comment:** For completeness and to align with Condition 5, Type II changes should be added. **Proposed Change:** Introduce the following variation sub-category: **g) Implementation of a new test method involving a novel non-standard technique or a standard technique used in a novel way including replacement and addition** **Variation Type II**	
B.I.b.2.h		**Comment:** An additional subclass is needed to address cases of addition of a biological / immunological / immunochemical test procedure for a biological substance with no other changes to the test methods or to the specifications of the active substance.	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		<u>Proposed change</u>: **h) Addition of a biological / immunological / immunochemical test method for a biological substance with no other changes to the test methods or to the specifications and no consequences on the quality of the substance: type IB.**	
B.I.b.2 Condition 2		**Comment:** Replace current condition 2) *'There have been no changes of the total impurity limits; no new unqualified impurities are detected'.* In order to align with the terminology of B.I.b.1, sub-category h). Unclear condition *'no new unqualified impurities'.* The reference to the valid limits is sufficient; detection of unqualified impurities below the respective limit is acceptable. the term *"unqualified"* is not relevant for reagents/starting materials/intermediates **<u>Proposed Change</u>:** **<u>"No change of specification limits the method is controlling as a result of a safety or quality issue"</u>**	M
B.I.b.2 Condition 3		**Comment:** Replace: *'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)'.* More clarity would be beneficial. This could be achieved by reference to the method principles described in Ph. Eur. In combination with conditions 1 and 7, an appropriate control of the method performance is achieved. Such changes would include, for example HPLC to UPLC; stationary phase, mobile phase components and mode (gradient versus .isocratic) in LC; GC carrier gas or detector, detection mode or labelling dye for CE-SDS, laser light diffraction from one to another instrument manufacturer, Atomic Absorption Spectroscopy to ICP-OES, provided that the same	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		validation criteria can be applied and therefore the same performance is ensure. **Proposed change:** **"Method principle remains within the same pharmacopoeial general test chapter"**	
B.I.b.2 Condition 4		**Comment:** Replace ' *(does not include standard pharmacopoeial microbiological methods'* The reference to the relevant Ph.Eur. chapters would provide more clarity. **Proposed change:** "The test method is not a biological/immunological/immunochemical method or a method using a biological reagent **as listed in Ph. Eur. Sections 2.06 and 2.07."**	M
B.I.b.2 Condition 8 (new addition)		**Comment:** The adjusted method must conform to the same method controls (e.g. system suitability test limits). **Proposed change:** Introduce new condition 8: **"Condition 8: Appropriate method controls must be in place and the same limits applied, e.g. system suitability limits (such as resolution of the most critical peak pair)"**	M
B.I.b.2 Condition 9 (new addition)		**Comment:** As the same method principle needs to be kept for minor changes, also the same validation tests and criteria can be applied. This condition ensures an objective criterion for a minor change. **Proposed change:** Introduce new condition 9: **"Condition 9: The same validation tests and criteria can be applied."**	M
B.I.c.1		**Comment:** Condition 3 currently reads: "Sterile, liquid and biological / immunological active substances are excluded. This condition should better describe the product aspects that may impact the evaluation of this	e

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		type of change. The evaluation of changes to immediate packagings of solid non sterile biological active substances is currently not described. **Proposed change:** Reword Condition 3 as follows: "Sterile liquid chemical active substances and liquid biological/immunological active substances are excluded." Consider adding a further subcase d) Solid non-sterile biological active substances - should be a type IB (no condition) Replace "non-frozen" by "liquid" for harmonisation of the rest of the variation text.	
B.I.c.2		**Comment:** The widening of the approved specifications is not envisaged in this variation. **Proposed change:** Add a further variation to describe the widening of the specifications.	
B.I.c.2.b		**Proposed change:** B.I.c.2.b) Addition or **replacement** of a ~~new~~ specification parameter to the specification with its corresponding test method	m
B.I.c.2.c		**Proposed change:** Please revise documentation item Nº. 5 / 6 to read as follows: [...] or a justification that it is obsolete or redundant.	m
B.I.c.2.d		**Proposed change:** State "as a result of a safety or quality issue" as a new condition, and as such move it into the "Conditions" column for variations B.I.c.2.d.	e
B.I.d.1.c		**Comment:** In the conditions to the new category "Change to an approved stability protocol", it is stated that "The changes do not concern a widening of the acceptance criteria in the parameters tested, a	m

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		removal of stability indicating parameters or a reduction in the frequency of testing." Indeed changes to the specification would be covered by B.I.b.1 Please clarify: Widening of acceptance criteria is covered by B.I.b.1 In Condition2 a reduction of frequency of testing should be deleted as it can happen that it is justified. This point should be understood as being in documentation 4. It is unclear why a new sub-category for a *'Change to an approved protocol'* has been introduced. We assume this would only apply if a protocol was submitted and not for stability tables submitted and testing to be carried out to ICH. Clarification is needed. Further clarity on instances where this would be applied is needed. **Proposed change:** Condition 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.~~	
B.I.e.1.a		**Comment:** Revise to align with B.II.g.1.a **Proposed change:** "One **or more** unit operation**s** in the manufacturing process of …"	m
B.I.f.1		**Comment:** Documentation 3: According to Questions and answers on post approval change management protocols (EMA/CHMP/CVMP/QWP/586330/2010 dated March 30, 2012), "At the time of submission of the protocol (Type II) only 3.2.R/2.3.R. is affected (or Part 2.G for veterinary applications). Update of the relevant section(s) of Module 3 (other than 3.2.R) is done with the Type I (A or B) variation to implement the protocol". Therefore, it is not consistent to state as documentation 3, that we have to provide with "amendment of the relevant section(s) of the dossier". Update of relevant sections must await the implementation of the change and be submitted at implementation covered by B.I.f.4.	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
B.I.f.2		**Comment:** There is no need to have a Condition applied to the deletion of a protocol. Whether or not there are unexpected events or OOS, the protocol could be deleted by Type IA_{IN}. The Agency can always request more information after submission of the Type IA_{IN} if there are concerns regarding the proposed deletion. There is no risk to patients since the change will not be implemented in either case. **Proposed change:** Remove the Condition from this section.	M
B.1.f.3		**Comment:** Documentation 1 states: "Declaration that an assessment of comparability is not required for biological/immunological medicinal products". This is almost impossible since process changes mostly require a comparability exercise and contradicts the Q+A on PACM which states regarding the content of the PACM protocol: "For biologics, the approach to be used to demonstrate the comparability of the pre- and post- change product" In the Documentation, a "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." is required for minor changes to an approved change management protocol, and the change is categorized as Type IB. In other categories, changes within the approved limits are regarded as not effecting the quality, safety and/or efficacy of the drug product, and are categorized as Type IA (or IA_{IN}) therefore, it is not clear, why minor changes to the post-approval change management protocol within the approved limits need to be filed as Type IB variation. **Proposed change:** Documentation 1: ~~In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products~~	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		Comment: The terms '*major*' and '*minor*' are subject to interpretation and should be avoided. **<u>Proposed change</u>:** (a) to be reworded as "<u>Changes to an approved post approval change management protocol that fundamentally change the content or approach of the protocol'</u> (b) to be reworded as "<u>Changes to an approved post approval change management protocol that do not fundamentally change the content or approach of the protocol.</u>**<u>"</u>** Additionally, it is suggested to add the Note regarding minor changes reflecting updated analytical tests and limits, which accompanies B.II.h.4, to this change as well. **Comment:** Missing documentation 2: <u>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)</u>	
B.1.f.4		**Comment:** The variation category should be re-worded. Currently the variation is classified as "Implementation of changes foreseen in an approved change management protocol....." It should be modified to state "Implementation of changes included in an approved change management protocol....." **Comment:** For B.1.f.4 c and d condition 1 should apply. For B.1.f.4 documentation 2 delete the requirement for a declaration that an assessment of comparability is not required for biological/immunological medicinal products, since the CMP is a typical filing that is preferred for major changes in the manufacturing process or addition of new manufacturing site. In these cases an assessment of comparability is required and there would be	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		no advantage any more to use the CMP concept. Contradicts the Q+A on PACM which states regarding the content of the PACM protocol: "For biologics, the approach to be used to demonstrate the comparability of the pre- and post- change product" Implementation of a change according to a change management protocol should be evaluated case by case and not according to type of product (biological) **Proposed change:** c) Conditions to be fulfilled: 1 d) Conditions to be fulfilled: 1 Documentation 2: ~~In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products~~ ~~d) Implementation of a change for a biological/immunological medicinal product.~~ **Comment:** B.I.f.4.a) and B.I.f.4.b): A definition is lacking, when immediate notification and when annual report rules apply to the implementation of a change following an approved change management protocol. Comparing both categories, it is not clear, which conditions must be fulfilled by the applicant to either file the implementation of a change immediately (=B.I.f.4.a)) or within 12 months (=B.I.f.4.b)). It should be defined, which conditions must be fulfilled. For subcategories B.I.f.4.a) and B.I.f.4.b) an amendment to the relevant sections of the dossier should be made; from a manufacturers point of view, this will include all relevant data from the studies performed in accordance with the approved change management protocol (see Documentation No.3 and No.4).	

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		Categories are distinguished by the need for "further supportive data", however, it is not clear from the conditions to be fulfilled and the documentation to be submitted, what the definition for "further supportive data" is. Need further guidance of when submitting supportive data and when not. If these results are declared as related to documentation no. 4, the applicant may file the change as Type IA or $IA_{IN.}$ If the same results are declared as Documentation No. 3, the change must be classified as Type IB. **Proposed change:** 1) Add additional condition for sub-categories B.I.f.4.a, B.I.f.4 (b) – new Condition "2. The protocol is not relating to a biological/immunological product" 2) add additional text in brackets to the description of sub-category B.I.f.4 (c)**:** "… (in a protocol not relating to a biological/immunological product)"	M
B.1.f.4.b		**Comment:** Typo: data' lacks in the sentence ' … no further supportive....' **Proposed change:** b) The implementation of the change requires further supportive data and should be notified to the competent authorities within 12 months of implementation.	e
B.1.f.4.d		**Comment:** Is it possible to specify for this case whether it is with further supportive data or without supportive data? Or does it cover both cases? This variation type implies that it concerns all PACMPs for a biological/immunological medicinal product as Type IB variation. However, biological/immunological medicinal products should also be able to use B.I.f.4.a) and b) (Type IA variations) if applicable and with reference to documentation to be supplied no. 2 does not warrant an assessment of comparability. The implementation variation type will be agreed with the Agency at the time of the approval of the initial PACMP	M
NEW		**Comment** Would it be possible to create a new variation for the following change: "Substantial change to the	

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		restricted part of an ASMF" We propose the category of a Type II.	
B.II.a.3.a		**Comment:** *Changes in the components of the flavouring or colouring system.'* **Proposed change:** *"Changes in the components of the flavouring, **coating** or colouring system."*	e
B.II.b.1		**Comment:** Documentation – The application form referred to in is the new MA application form and not the current variation application form. This information is generally poorly maintained once the MA has been authorised and the contact details become subject to Manufacturing Authorisation maintained by the Competent Authority Inspectorate. There seems to be little value in maintaining this part of the New MA application form as well as module 3.2.P.3.1. A flow chart/schematic illustrating supply chain and site interaction with the product is also required at time of initial MA application. It would be valuable to maintain this document and therefore add it as a document requirement. Documentation 3. Clear Present versus Proposed in the variation application form 4. Updated dossier modules 5. Revised schematic of product flow between sites It is not clear why a product manufactured successfully for a considerable period within an organisation would need to be managed a s Type II change IF the site change is within the same manufacturing group EVEN if the process was originally considered 'complex'. The history of effective manufacture should allow the change to be managed as a Type I change.	M M
B.II.b.1.c		**Comment:** c) The term complex manufacturing processes is not precise enough, because this depends on	m

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		company experiences. Therefore this should be clarified or deleted.	
B.II.b.2		**Comment:** - Why is importer added? We do not have it included in our registration dossier or does this become a requirement? Why not make it clear that it is also for stability testing sites since it is a requirement to have them listed in the CTD sections?	e
B.II.b.2		**Comment:** New condition (5) item added to B.II.b.2: "At least one batch control/testing site remains within the EU/EAA or in a country where an operational and suitably scoped GMP mutual recognition agreement (MRA) exists between the country concerned and the EU, that is able to carry out product testing for the purposes of batch release within the EU/EEA." Proposed change (if any): condition should be expanded to also allow testing at a site outside the EU/EEA, with no MRA, but that has been issued a GMP certificated within the last 3 years by a EU/EEA competent authority.	M
B.II.b.2		**Comment:** Type II required for all changes to quality control testing arrangements for biologic involving biological methods Proposed change (if any): Propose an exception (lower variation classification) for standard pharmacopoeial microbiological methods	M
B.II.b.2.b		**Comment:** Change to B.II.b.2 (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 A change to a QC site for a non-biological is a Type IA (all tests). This effectively upgrades a change for a biological test by two levels i.e. Type IA to Type II. Previously, this Type of change would only have been upgraded by one level i.e. to a Type IB (Type IA defaulting to Type IB, due to the exclusion of biologicals).	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		Proposed change: - B.II.b.2 (b) classified as a Type IB variation. Condition 3 "the product is not a biological…" is removed from B.II.b.2 (a), to allow transfer of non-biological tests (e.g. pH) as Type IA variations.	
B.II.b.2		**Comment:** Concerning *Change to importer, batch release arrangements and quality control testing of finished product* **Proposed change:** condition 3: we suggest removing this specific condition for biologics due to scientific considerations. **Comment:** The definition of "an importer" is not clear. **Proposed change:** Please clarify what functions are considered to define an importer.	M M
B.II.b.2.c.2		**Comment:** This used to be categorised as type 1A(IN) and is now categorised as type II. If the conditions 1 to 5 are met and GMP requirements are in place (according to listed Documentation), this change should remain as type 1A(IN). If conditions 1-5 are not met, then it should be a default type 1B. **Proposed change:** c) Replacement or addition of a manufacturer responsible for importation and/or batch release 2. Including batch control/testing Type IA(IN) This change should remain IA_{IN}. As biological/immunological products are excluded there is no reason for an upgrade to Type II. It is suggested to take out condition 4.	M M
B.II.b.2.c.3		**Comment:** If the B.II.b.2.c variation remains a type II variation, then, the addition of this third variation seems redundant. This variation then already falls within the scope of the B.II.b.2.c.2 variation.	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		Comment: Variation B.II.b.2(c).3 related to a site of testing for biological methods upgraded to a Type II is too stringent and seems disproportionate. When we previously submitted this change, it was assigned a type IB (by default) category B.II.b.2(c)1 as condition 2 (the product is not a biological/immunological product) was not met. It is unclear what data would be needed to support this Type II variation as method transfer documents are generally considered GMP information subject to inspection and could still be submitted, if required, as part a Type 1B variation. **Proposed change:** New category B.II.b.2(c).3 should be deleted and changes to a site of quality control testing using biological methods should be handled as a TypeIB (by default) category B.II.b.2(c)1 variation	
B.II.b.3		**Comment:** Concerning *Change to the manufacturing process of the finished product…* **Proposed change:** condition 2: we suggest removing this specific condition for biologics due to scientific considerations.	M
B.II.b.3		**Comment:** Documentation 5 – Add word "risk" **Proposed change:** From:"....has been accepted as part of a previous assessment where...." To:"....has been accepted as part of a previous risk assessment where...."	e
B.II.b.3		**Comment:** Type IB variations should be defined as not meeting a condition for a Type IA submission where a Type II variation is not assigned. **Proposed change:**	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		Consider rewording category a) to state: a) Minor change in the manufacturing process <u>of the finished product</u> Then add a condition to define those situations where a default Type IB due to the condition not being met e.g. aqueous oral suspension, parenteral or other sterile preparation, biotech product not needing an assessment of comparability etc.	
B.II.b.3		**Comment:** Why not add: Other variation z : Minor changes in the manufacturing process of an immediate release sterile product as a type IB change?	e
B.II.b.3		Same comment as B.I.a.4.g and B.II.b.3 in relation to changes to non-critical process parameters	M
B.II.b.3.c		**Comment:** The current wording of B.II.b.3.c *("The product is a biological/immunological medicinal product and the change requires an assessment of comparability"*), and foresees a Type II procedure. Our reading is that minor changes to manufacturing processes which do not require an assessment of comparability could be considered as Type IB by default. However, we believe that it would be clearer, would facilitate the reading of the guideline and would limit risks of misinterpretation, if a specific sub-category for such minor changes would be added explicitly stating that a Type IB procedure applies. **<u>Proposed change</u>:** 1) Reword the description of sub-category B.II.b.3 (c) as follows: *"The product is a biological/immunological medicinal product and the change **<u>may have a significant impact on quality, safety and efficacy and</u>** requires an assessment of comparability" - Procedure type : II* 2) Add a further variation under B.II.b.3 for submission of minor variation to biological product manufacturing processes as follows: ***<u>"The product is a biological/immunological medicinal product and the change does not require an assessment of comparability"</u>*** - Procedure type: **IB.**	M
B.II.b.3 **B.II.b.5**		**Condition 8 for all** **Comment:**	C

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		The wording 'enhanced development approach', is not clear. What are the criteria? A definition may be helpful. **Proposed change:** This refers to an *'acknowledged enhanced development approach'*. It would be better to refer to relevant terminology used in ICH Q8 (R2) and Q10 to avoid confusion. Condition 9 for all **Comment:** The wording 'an already approved monitoring scheme', is not clear and may cause confusion. By adding the words 'quality system' this provides a clear link to ICH Q10 **Proposed change:** The effect of the proposed change has been evaluated using an already approved monitoring scheme or **quality system** and the process parameter in question remains non critical **Documentation 5/Documentation 8** **Comment:** Clarity on expectations on what would need to be submitted to fulfil the condition "Documentary evidence that, that the non-criticality of the parameter has been accepted as part of a previous assessment where the enhanced development approach in the development and optimisation of the manufacturing process concerned is formally acknowledged."	
B.II.b.3.g **B.II.b.5.g**		**Comment:** Change to non-critical processes parameters, where the process has been developed and optimised using an enhanced development approach for the particular manufacturing step. This type of change would normally be dealt within a GMP system. Why does the applicant now need to communicate non-critical process parameters? Presuming an enhanced development approach is referring to design space/quality by design this	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		change seems to be counterproductive. The wording also indicates that this is only applicable to products manufactured within a design space and would not apply to older products. Consider removing this additional classification. **Documentation 3** **Comment:** For non-critical process parameter changes that do not affect dissolution, why would it be mandatory to provide comparative dissolution? **Proposed change:** Remove the mandatory requirement for documentation 3. **Comment:** Does it also cover change in validation parameters registered as "production" parameters (parameters only used in validation)? Define "non critical" Define "enhanced"	
B.II.b.3.z		**Comment:** Article 5 recommendation not included in the revision: Type IA Change in the packaging material of bulk product not in contact with the bulk product formulation (including replacement or addition) Condition 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.	m

Variations reference	Stakeholder number ***(To be completed by the Agency)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
B.II.b.4		**Comment:** It should be considered how to classify the more than 10-fold increase of batch size for a non-sterile liquid or semi-solid preparation for cutaneous application (which are usually not manufactured according to a complex manufacturing process). Is it a variation type IB unforeseen? It is not clear why the case e) is only applicable to immediate release (oral) pharmaceutical forms and cannot apply for these other forms? **Proposed change:** Consider to apply this category to more pharmaceuticals forms that are not manufactured to a complex manufacturing process.	M
B.II.b.4		**Comment:** Condition 7 It is not appropriate to mention BE in the context of batch scale. For batch size increase above factor 10, no BE study is normally required. This is only an issue moving from pilot scale to production scale.	C
B.II.b.4.e.		**Comment:** The addition of "oral" is not understood. What about injectables produced according to non-complex manufacturing process? This is not listed so could also be a Type IB by default.	e
B.II.b.5		**Comment:** Same comment as the one related to B.1.a.4 g) **Proposed change:** Delete: "*Change to the limits of non critical process parameters, where the process has been developed and optimised using an enhanced development approach for the particular manufacturing step(s) Type IA"*	C
B.II.b.5		**Comment:** Concerning Change to in-process tests or limits applied during the manufacture of finished product. **Proposed change:** Add (b) addition of new tests and limits, condition 6: we suggest removing this specific condition	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		for biologics due to scientific considerations. **Comment:** As for active substance above, it is not clear what the difference is between a non critical parameter with an IPC limit and a non critical parameter with an approved monitoring system. Clarification is needed. **Documentation 8** **Comment:** What '*documentary evidence'* would be considered appropriate? Additional clarity required. **Condition 7** **Comment:** It is an unclear condition to state list parameters with e.g. Delete examples. There should be an option to "replace" a method. Some markets request 2 variations for this, to delete and add.	C M
B.II.b.5.g		**Comment:** Same comment as B.I.a.4.g and B.II.b.3 in relation to changes to non-critical process parameters.	M
B.II.c.1		**Comment:** Condition 1: is it possible to precise that the commitment is a MAH commitment? Align (d) with (e) and add "which may have a significant effect on the overall quality of the finished product"	m m
B.II.c.1.b		**Comment:** It would be consistent to add to the wording of this variation "Addition **<u>or replacement</u>**" to be consistent with variation B.II.c.1.f) which is to be used in case of safety or quality issues, but there are many cases where there is no such issue.	e
B.II.c.1.f		**Comment:** The change should not be listed as a Type IB. Instead a condition that the corresponding Type IA (B.II.c.1.b) cannot meet should be introduced.	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		Delete B.II.c.1.f and add a new condition (8) that it is not a result of a quality or safety issue.	
B.II.c.1.g		**Comment:** To clarify what is meant by "non-official pharmacopoeia"? Current best practice (in order of preference): PhEur, Member State Pharmacopoeia e.g. BP, FrP etc, USP/USNF, JP	C
B.II.c.2.c **B.II.d.2.c**		**Comment:** The word "substantial" should be changed to "Major" to clearly define this as a Type II variation which directly refers to the Type II variation classification as indicated in the variations regulation EC 1234/2009 (Major – has a significant impact on quality, safety and efficacy).	C
B.II.c.2 Category a)		**Proposed change:** Introduce addition condition 9 for sub-category a) (see below for details).	
B.II.c.2 Category e) (New)		**Comment:** In order to improve clarity, a distinction between adjustments and changes would be beneficial. Adjustment ranges are either defined in Ph.Eur. chapter 2.2.46 for chromatographic methods, or should be registered and covered by validation data. **Proposed Change:** Introduce the following variation sub-category, with new condition: **e) Adjustments as allowed by the compendia or within registered and validated ranges** **Condition 7: (see below)** **Variation Type IA**	
B.II.c.2 Category f)		**Comment:** For completeness and to align with Condition 6, Type II changes should be added.	

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
(New)		**Proposed Change:** Introduce the following variation sub-category: **f) Implementation of a new test method involving a novel non-standard technique or a standard technique used in a novel way including replacement and addition** **Variation Type II**	
B.II.c.2 Condition 2		**Comment:** Replace current condition 2: ' There have been no changes of the total impurity limits; no new unqualified impurities are detected'. In order to align with the terminology of B.I.b.1 sub-category h). Unclear condition *'no new unqualified impurities'.* The reference to the valid limits is sufficient; detection of unqualified impurities below the respective limit is acceptable. **Proposed Change:** **"No change of specification limits the method is controlling as a result of a safety or quality issue"**	M
B.II.c.2 Condition 3		**Comment:** Replace: *'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)'.* More clarity would be beneficial. This could be achieved by reference to the method principles described in Ph. Eur. In combination with conditions 1 and 7, an appropriate control of the method performance is achieved. Such changes would include, for example HPLC to UPLC; stationary phase, mobile phase components and mode (gradient vs.isocratic) in LC; GC carrier gas or detector, detection mode or labeling dye for CE-SDS, laser light diffraction from one to another	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		instrument manufacturer, Atomic Absorption Spectroscopy to ICP-OES, provided that the same validation criteria can be applied and therefore the same performance is ensure. **Proposed change:** **"Method principle remains within the same pharmacopoeial general test chapter"**	
B.II.c.2 Condition 4		**Comment:** Replace *'.... (does not include standard pharmacopoeial microbiological methods.'* The reference to the relevant Ph.Eur. chapters would provide more clarity. **Proposed change:** "The test method is not a biological/immunological/immunochemical method or a method using a biological reagent **as listed in Ph. Eur. Sections 2.06 and 2.07."**	M
B.II.c.2 Condition 6 (New addition)		**Proposed change:** Introduce new condition 6 for sub-category d) as follows; **"Any new test method does not concern a novel non-standard technique or a standard technique used in a novel way."**	M
B.II.c.2 Condition 7 (New addition)		**Comment:** The adjusted method must conform to the same method controls (e.g. system suitability test limits). **Proposed change:** Introduce new condition 7: **"Condition 7: Appropriate method controls must be in place and the same limits applied, e.g. system suitability limits (such as resolution of the most critical peak pair)"**	M
B.II.c.2 Condition 8 (New		**Comment:** As the same method principle needs to be kept for minor changes, also the same validation tests and criteria can be applied. This condition ensures an objective criterion for a minor change.	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
addition)		**<u>Proposed change</u>:** Introduce new condition 8: **"Condition 7: <u>The same validation tests and criteria can be applied."</u>**	
B.II.c.4		**Comment:** Please clarify how long a novel excipient is expected to be considered novel? For example until the first renewal. **<u>Proposed change</u>:** Delete novel excipient and revert to original wording and instead control within the quality management system.	C
B.II.c.5		Comment: There is no variation to cover the change to manufacturer of the novel excipient that is not part of the same group as currently approved but specifications, method of preparation and route of synthesis are identical to those approved. **<u>Proposed change</u>:** Additional type IA(IN) The proposed manufacturer is not part of the same manufacturing group as the currently approved manufacturer. Needs to comply with the conditions 1-3 and documentation requirements 1-6.	M
B.II.c.5		**Comment:** Please clarify how long a novel excipient is expected to be considered novel? For example until the first renewal. **<u>Proposed change</u>:** Delete B.II.c.5 in its entirety and instead control within the quality management system.	C
B.II.c.5		**Comment:** Where the manufacturer is not part of the same pharmaceutical group is not covered **<u>Proposed change</u>:**	m

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		"***B.II.c.5 (d) The proposed manufacturer is not part of the same pharmaceutical group as the currently approved manufacturer – Type IB".***	
B.II.c.5.c		**Comment:** Change (c) is introduced [Introduction of a new manufacturer of a biological novel excipient] as a Type II variation without it being clear what a 'biological novel excipient' is. Is this a novel excipient for a biological product or an excipient of biological origin ? Is an excipient sourced from biological source but modified synthetically a 'novel biological excipient'? Suggest this new term needs definition in a glossary.	M
B.II.d.1		**Comment:** Condition 6 states '.or a method using a biological reagent for a biological active substance' – since this is the section for finished product this should read ''..or a method using a biological reagent for a biological product'. **Comment:** Condition 8 is not very clear. Would it be possible to re-word it? **Comment:** We suggest adding a sub-category *"Widening of the approved specifications limits"* to align with what is foreseen for the active substance (sub-category B.I.b (g)) **Proposed change:** New sub-category "***B.II.d.1(j): Widening of the approved specifications limits, which may have a significant effect on the overall quality of the finished product"*** - Procedure type : **II**	e e M
B.II.d.1		**Comment:** It should be specified in the main text of this variation category that it also applies to intermediates if described in the dossier. **Proposed change:** "B.II.d.1 Change in the specification parameters and/or limits of the finished product **or**	e

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		intermediates (if described in the dossier)".	
B.II.d.1.d		**Comment:** Could this change also include the "coloration nuance" in the descriptive list? Clarification needed as to why this test would need to be made an example? Would condition 9 be sufficient to classify this test?	
B.II.d.1.d		Proposal to add the text in " ": Such as odour and taste or identification test for colouring or flavouring material, "or parameters which are sufficiently controlled via an in-process-test [e.g. hardness or friability]" Condition 9: Acc. to ICH Q6A it is normally appropriate to perform hardness and/or friability testing as an in-process control under these circumstances, it is normally not necessary to include these attributes in the specification. Thus, these parameters should not be listed per se as critical. Revise to state **Deletion or reducing the frequency of testing of a non-significant specification parameter (e.g. deletion of an obsolete or redundant parameter)** The example "odour "should be moved to condition 9 Clarification that this is not conflicting with ICH guidance on stability testing and/or ICH bracketing and matrixing study designs. i.e. frequency according to ICH (every 3 m for first year, then every 6m, and then annually) and if the applicant can fully demonstrate (with stability data from 'n' studies) that there is no longer a need for full testing time point every 3m for first year is a submission really required make this change? Or does the classification guidance intend to refer frequency in terms of tests which may be performed on at least 1 batch per year where sufficient data are collected to consider this test as not required on every production batch? AND Dropping specific tests at particular time points on a single batch (not part of a bracketing or matrixing design).	M M
B.II.d.1.e		**Comment:**	

Variations reference	Stakeholder number ***(To be completed by the Agency)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		The text should specify that a Type II procedure should only apply when the change is expected to have a significant impact on the overall quality of the finished product. We suggest using similar language as for the active substance, sub-categories B.I.b.1 (f) and (g). **Proposed change:** *"e) Change outside the approved specifications limits range for the active substance**, which may have a significant effect on the overall quality of the finished product**".*	M
B.II.d.1.h **B.II.d.2.e**		**Comment:** These new classifications should be clarified or removed. The current EU variation classification guideline EC 2010/C 17/01 states (Page 3 paragraph 2 of word document or OJ Page 2 col 2 paragraph 2): 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. The new classifications increase the regulatory burden and are non-value added for pharmacopoeial methods. Therefore implying that if we change within 6 months to comply with the pharmacopoeia no submission is required. If not implemented within 6 months then: Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur for the finished product Procedure type ~~*1A$_{IN}$*~~ *IA*	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
B.II.d.1.i		**Comment:** UDU is too specific for the classification guideline and should remain in the Article 5 classification otherwise it could cause many concerns with any update to the Ph.Eur. as to whether a more detailed explanation is required. It is unclear why a change to align with this pharmacopoeial change needs to be managed as a Type IB change rather than a Type IA. **<u>Proposed change</u>:** It is recommended that this change is written in a more GENERALISABLE way (e.g. Change to a newly introduced Ph.Eur. method from a prior Ph.Eur. method. Align (f) and (g) and add "which may have a significant effect on the overall quality of the finished product" Introducing a stronger position statement to better advise when applicants should apply for a article 5 recommendation/classification allowing more flexibility in utilising z category non article 5 submissions left to the discretion of the applicant and subject to validation. For example: Category Z Type IA – Should be used for simple administrative changes requiring minimal technical validation. No technical data should be provided. Category Z Type IB – Should be used for Complex administrative changes and technical submissions where a basic to moderate level of detail data package has been submitted for technical review and a technical/scientific review is required. Category z Type II – for complex technical changes where an in depth technical/scientific review will be required and the variation is supported by a moderate to complex level of detail data package. For borderline cases where the applicant believes the validator could refer their submission for an article 5 recommendation then it is in the interest of the applicant to apply for the article 5 recommendation in advance of any submission. Introduces change (i) [PhEur 2.9.40 UDU is introduced to replace the currently registered method…}. Two comments on this – it is unclear why a change to align with this pharmacopeoial	M M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
B.II.d.1.i		**Comment:** New category has been introduced as type IB variation: It is the opinion of the EMA as released to the public on the EMA homepage, that from a pharmaceutical quality point of view, the approach taken in the harmonised general chapter on uniformity of dosage units (2.9.40) is considered equivalent to what was previously required in the Ph. Eur. through the general chapters on uniformity of mass of single-dose preparations (2.9.5) and uniformity of content of single-dose preparations (2.9.6). These general chapters, 2.9.5 and 2.9.6, are still included in the current version of the Ph. Eur. Taking this into account, the decision on what approach to take is left to the applicant. Application of either the Ph. Eur. harmonised general chapter on uniformity of dosage units (2.9.40) or the Ph. Eur. general chapters on uniformity of mass of single-dose preparations (2.9.5) and uniformity of content of single-dose preparations (2.9.6) are both considered acceptable options to demonstrate compliance with the Ph. Eur. with regard to uniformity of dosage units. Following the outline of these arguments, it should be clarified that no Type IB is to be submitted if the MAH complies with either chapter 2.9.40 or 2.9.5/2.9.6. **Proposed change:** Although classified in an article 5 procedure, the change should be reclassified as type IA, or inclusion of this specific change into the subcategory B.II.d.1.h).	M
B.II.d.1 (additional sub-category)		**Comment:** Add a sub-category Widening of the approved specifications limits to align with what is foreseen for the active substance (sub-category B.I.b.g) **Proposed change:** New sub-category **B.II.d.1(j): "Widening of the approved specifications limits, which may have a significant effect on the overall quality of the finished product"** - Procedure type : **II**	

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
B.II.d.1.h		**Comment:** It would be useful to have the same change reflected in the active substance section B.I.b.2**.**	m
B.II.d.2		**Comment:** Condition 1: Clarify what is meant by "Appropriate validation studies have been performed". Add a footnote to reflect the meaning of condition 1. Different companies have different policies on what level of detail is submitted for analytical procedures. Method validation expectations are aligned by ICH. Therefore, a change to non pharmacopoeial analytical method is reportable when appropriate re-validation studies have been performed. Changes that do not require a revalidation exercise should be documented in the quality management system.	M
B.II.d.2.c		**Comment:** The added word to B.II.d.2.c "substantial" to this category suggests that non-substantial, ie minor changes of a biological/immunological/immunochemical test methods or a method using a biological reagent be filed as a Type IA or Type IB. **Proposed change:** g) Minor changes of a biological/immunological/immunochemical test methods or a method using a biological reagent. Conditions to be fulfilled: 1, 2, 3 Documentation to be supplied: 1, 2 Procedure type: IB	M
B.II.d.2.c		**Comment:** Substantial change to or replacement of a biological / immunological / immunochemical tests method or a method using a biological reagent or replacement of a biological reference preparation not covered by an approved protocol. **Proposed change:**	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		B.II.d.2 should also include a category for minor changes to testing, storage of reagents (if no change to specification) and detail is registered in the dossier (propose Type IA).	
B.II.d.2 (g)		**Comment:** In order to improve clarity, a distinction between adjustments and changes would be beneficial. Adjustment ranges are either defined in Ph.Eur. Chapter 2.2.46 for chromatographic methods, or must be registered and covered by validation data. **Proposed Change:** Introduce the following variation sub-category, with new condition: **g) Adjustments as allowed by the compendia or within registered and validated ranges** **Condition 6: (see below)** **Variation Type IA**	M
B.II.d.2 (h)		**Comment:** In order to align with B.II.d.1, a new variation sub-category needs to be introduced. **Proposed Change:** Introduce the following variation sub-category: **g) Implementation of a new test method involving a novel non-standard technique or a standard technique used in a novel way including replacement and addition** **Variation Type II**	M
B.II.d.2 Condition 2		**Comment:** Replace : *'There have been no changes of the total impurity limits; no new unqualified impurities are detected'* In order to align with the terminology of B.II.d.1' *Change*	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		in the specification parameters and/or limits of the finished product,' sub-category h). Condition 2 is unclear *'no new unqualified impurities are detected.'* The reference to the valid limits is sufficient, detection of unqualified impurities below the respective limit should be acceptable. **Proposed Change:** **"No change of specification limits the method is controlling as a result of a safety or quality issue"**	
B.II.d.2 Condition 3		**Comment:** Replace: *'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)'* More clarity would be beneficial. This could be achieved by reference to the method principles described in Ph. Eur. In combination with conditions 1 and 7, an appropriate control of the method performance is achieved. Such changes would include, for example HPLC to UPLC; stationary phase, mobile phase components and mode (gradient versus .isocratic) in LC; GC carrier gas or detector, detection mode or labelling dye for CE-SDS, laser light diffraction from one to another instrument manufacturer, Atomic Absorption Spectroscopy to ICP-OES, provided that the same validation criteria can be applied and therefore the same performance is ensure. **Proposed change:** **"Method principle remains within the same pharmacopoeial general test chapter"**	M
B.II.d.2 Condition 4		**Comment:** Replace ' *(does not include standard pharmacopoeial microbiological methods'* The reference to the relevant Ph.Eur. chapters would provide more clarity.	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		Proposed change: "The test method is not a biological/immunological/immunochemical method or a method using a biological reagent **as listed in Ph. Eur. Sections 2.06 and 2.07."**	
B.II.d.2 Condition 6 (New addition)		**Comment:** The adjusted method must conform to the same method controls (e.g. system suitability test limits). **Proposed change:** Introduce new condition 6: **"Condition 6: Appropriate method controls must be in place and the same limits applied, e.g. system suitability limits (such as resolution of the most critical peak pair)"**	M
B.II.d.2 Condition 7 (New addition)		**Comment:** As the same method principle needs to be kept for minor changes, also the same validation tests and criteria can be applied. This condition ensures an objective criterion for a minor change. **Proposed change:** Introduce new condition 7: **"The same validation tests and criteria can be applied."**	M
B.II.e.1.b		**Comment:** As reworded in the new Commission proposal, this sub-category seems now to imply that the addition of a new container for sterile medicinal products and biological/immunological medicinal products is to be processed as a Type II variation (e.g. the addition of a glass pre-filled syringe container in addition to an existing glass vial presentation for a vaccine). Although we support the classification of such a change as a Type II procedure, this appears in contradiction with what is advised in the Commission Guideline on the categorisation of New Applications (NA) versus Variations Applications (V) (October 2003), where such a change is considered as a line extension. **Proposed change:**	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		We welcome the proposed re-wording in the Commission variations classification guideline and would recommend updating the 2003 Guideline on the categorisation of New Applications (NA) versus Variations Applications (V) to reflect this.	
B.II.e.1.b.3		**Comment:** It is proposed to create B.II.e.1.c) for this change instead of including it under B.II.e.1.b.3 as it does not concern either a change or addition of a new container and as such, does not fall within the scope of B.II.e.1.b. category.	
B.II.e.5		**Comment:** The additional documentation number 4) seems to be a condition rather than a request for documentation to be supplied. Otherwise, the way in which this should be documented should be specified. **<u>Proposed Change</u>:** Move the following to "Conditions", as new point 4: *4) In case of multipack/ bundle pack, the multipack/ bundle pack must ensure that the packs remain together during transportation and in pharmacy and should contain all legally required labelling items for the outer packaging, including blue-box (BB) information. In addition, it should comply with the applicable guidance at EMA/CMD level.* Should this not be a condition rather than documentation to be submitted and if it really should be documentation to be submitted what kind of documents should be provided: samples, mock-ups?	m
B.II.e.7		**Comment:** There is no classification for when a currently registered packaging supplier changes their name or address **<u>Proposed change</u>:** Deletion or change of name or address of a supplier	
B.II.f.1.c		**Comment:** For some reason, there is no sub-category under B.II.f.1 covering changes in shelf-life for biological medicinal products, when the stability studies have not been performed in accordance	

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		with an approved stability protocol. We suggest covering this under sub-category (c). **<u>Proposed change</u>:** "c) Change in storage conditions **or shelf-life** for biological medicinal products, …"	
B.II.f.1.e		**Comment:** We assume this would only apply if a protocol was submitted and not for stability tables submitted and testing to be carried out to ICH. Clarification is needed**.** At present any changes would be managed by internal change controls, as part of a Company's Pharmaceutical Quality System. **Comment:** It is unclear why a new sub-category for a '*Change to an approved protocol'* has been introduced. We assume this would only apply if a protocol was submitted and not for stability tables submitted and testing to be carried out to ICH. Clarification is needed. Further clarity on instances where this would be applied is needed - Condition 2 Clarification that this is not conflicting with ICH guidance on stability testing and/or ICH bracketing and matrixing study designs. i.e. frequency according to ICH (every 3 m for first year, then every 6m, and then annually) and if the applicant can fully demonstrate (with stability data from 'n' studies) that there is no longer a need for full testing time point every 3m for first year is a submission really required make this change? Or does the classification guidance intend to refer frequency in terms of tests which may be performed on at least 1 batch per year where sufficient data are collected to consider this test as not required on every production batch? AND Dropping specific tests at particular time points on a single batch (not part of a bracketing or matrixing design).	M M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		Comment: The proposed addition outside of post approval change management protocols described under B.II.h is interpreted as a new requirement for the submission of stability protocol. This brings additional constraints for the sites without any added value. This will result in loss of flexibility. **Proposed change:** We suggest the deletion.	M
B.II.h		**Comment:** Provision of revised module 3 components could prove difficult to manage in eCTD if the guideline does not clarify how these revised modules should be provided. Problems will arise if the proposed dossier modules are provided in the module 3 and could therefore overwrite registered commitments. Change management protocols (CMP) are required to be filed in 3.2.R. section of the eCTD. To prevent inadvertent overwriting of the registered commitments contained within 3.2.S and 3.2.P the proposed dossier modules should also be presented in 3.2.R. Replacement 3.2.S and 3.2.P modules are provided at the time of the Type IA or Type IB variation to present the data and outcome of the executed CMP. This should also be specified more precisely in the Change Management Protocol Q&A guidance document. http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500125400	M
B.II.h.2		**Comment:** There is no need to have a condition applied to the deletion of a protocol. Whether or not there are unexpected events or OOS, the protocol could be deleted by Type IA_{IN}. The Agency can always request more information after submission of the Type IA_{IN} if there are concerns regarding the proposed deletion. There is no risk to patient since the change will not be implemented in either case.	M

Variations reference	Stakeholder number ***(To be completed by the Agency)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		<u>Proposed change</u>: Remove the condition from this section.	
B.II.h.3		**Comment:** The terms '*major*' and '*minor*' are subject to interpretation and should be avoided. **<u>Proposed change</u>:** (a) to be reworded as "***<u>Changes to an approved post approval change management protocol that fundamentally change the content or approach of the protocol"'</u>*** (b) to be reworded as "***<u>Changes to an approved post approval change management protocol that do not fundamentally change the content or approach of the protocol."</u>*** Additionally, it is suggested to add a note regarding minor changes reflecting updated analytical tests and limits, which accompanies B.II.h.4, to this change as well. **Comment:** The requirement for a '*declaration that assessment of comparability for biological products is not required'* is not clear. Most PACM protocols for biological products will include an assessment of comparability, and the prospect to downgrade comparability assessments from Type II to Type IB is a primary driver behind the use of PACM protocols for such changes. **<u>Proposed change</u>:** Remove the "*declaration that an assessment of comparability is not required"* from the documentation for this change. **Comment:** Missing 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)	M C

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		Proposed change: "***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).”***	e
B.II.h.4		**Comment:** Please see above comment regarding "*declaration that an assessment of comparability is not required*." Same comment applies to this change. **Proposed change:** See B.II.h.3. **Comment:** As the reporting category for a biological is B.II.h.4 (d) (Type IB), then we recommend that for the sake of clarity and to avoid risks of confusion/misinterpretation an additional condition should be added for sub-categories B.II.h.4 (a) and B.II.h.4 (b). **Proposed change:** 1) Add additional condition for sub-categories B.II.h.4 (a), B.II.h.4 (b) – new ***"Condition 2. The protocol is not relating to a biological/immunological product"*** 2) add additional text in brackets to the description of sub-category B.II.h.4 (c): "*… **(in a protocol not relating to a biological/immunological product)"*** **Comment:** Implementation of a change according to a change management protocol should be evaluated case by case and not according to type of product **Proposed Change:**	C M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		Delete: d) Implementation of a change for a biological/immunological medicinal product The variation category should be re-worded. Currently the variation is classified as "Implementation of changes foreseen in an approved change management protocol....." It should be modified to state "Implementation of changes <u>included</u> in an approved change management protocol....."	M e
B.II.h.4		**Comment:** For B.II.h.4 c and d condition 1 should apply. For B.II.h.4 documentation 2 delete the requirement for a declaration that an assessment of comparability is not required for biological/immunological medicinal products, since the CMP is a typical filing that is preferred for major changes in the manufacturing process or addition of new manufacturing site. In these cases an assessment of comparability is required and there would be no advantage any more to use the CMP concept. Contradicts the Q+A on PACM which states regarding the content of the PACM protocol: "For biologics, the approach to be used to demonstrate the comparability of the pre- and post- change product" **<u>Proposed change</u>:** <u>c) Conditions to be fulfilled: 1</u> <u>d) Conditions to be fulfilled: 1</u> Documentation 2: ~~In addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products~~	M
B.II.h.4.a **B.II.h.4.b**		**Comment:** Since the conditions and documentation for sections a and b are identical there is no differentiating element between sections a and b. Therefore a differentiating element is missing. In addition like	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
B.II.h.4.c B.II.h.4. d		above the sentence "in addition, declaration that an assessment of comparability is not required for biological/immunological medicinal products" should be deleted If the classification is Type IA¬¬IN¬ and Type IA then there is no need to specify immediate notification or 12 mths given these are the known conditions associated with these classifications	e
B.II.h.4.a B.II.h.4. b		**Comment:** How to assess the degree of urgency to be notified "immediately" versus "within 12 months"? Would it be possible to clarify when we can consider to be falling under case a) versus case b)? This could be clarified in an additional Q&A.	m
B.II.h.4 (c)		**Comment:** This would benefit from further clarity on what a change is that requires further 'supportive data'. Further clarity required.	M
B.III.1.b. 5)		**Comment:** As the EDQM would have already evaluated this risk, we believe that a variation Type II is not justified. **<u>Proposed change</u>:** The change should be reclassified as type IA or IAIN, as defined for the certification procedure of the EDQM.	M
B.IV.1 Medical Device Documentation point 5		**<u>Proposed change</u>:** Add item d) to: "Change of a measuring or administration device" d) Addition or replacement of a device which is an integrated part of the primary packaging: 5. Documentation: add: For an integrated drug-device combination the device part should follow the same requirements as for CE marking, i.e. follow the essential requirements as well as quality systems requirements.	m

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
C. SAFETY, EFFICACY, PHARMACOVIGILANCE CHANGES			
C.I.1		**Comment:** Clarification is requested on the scope of variation C.I.1 and variation C.I.3. We support the addition of a reference to the Urgent Union Procedure (however we think that a reference to article 107i instead of 107g would be more appropriate). We question the addition of a reference to Article 107g which concerns PSUR and to Article 107q which concerns PASS. This appear to be overlapping implementation of changes following PSUR and PASS results already covered under the variation C.I.3. Please clarify. C.I.3. Clarification is requested on the case that a MAH is proactively submitting a variation application with the final PASS study report. Would the MAH require to still pay for a Type II variation? **Proposed change:** Revise the title: *Change in the Summary of Product Characteristics, Labelling or Package Leaflet following a procedure in accordance with Articles 30, 31, ~~107g~~, 107ik ~~or 107q~~ of Directive 2001/83/EC or Articles 34 or 35 of Directive 2001/82/EC or Article 29 of Regulation (EC) No. 1901/2006.*	C
C.I.3		**Comment:** We propose to modify the title of variation C.I.3 to include a clear reference to changes that have an impact on the product information. Under the new pharmacovigilance legislation a separate variation will no longer be requested for the implementation of changes to the MA for CAPs following the assessment of a PSUR or a PASS	C

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		report whereas for non-CAPs it will still be required to submit a variation for the implementation of changes resulting from the assessment of a PSUR or a PASS. We think that the asterisk note should be revised accordingly. Under the current variation C.I.3, some variation applications are perhaps being inappropriately classified as type II procedures rather than type IB procedures, e.g. variations following the assessment of PSUR, Post-Authorisation Measure without specific wording proposed by Competent Authority are being classified as a type II procedure even though these variations require minimal assessment such as: • As a consequence of the findings from a cumulative review a MAH was asked by the EMA to update the product information. There was no additional data to support this update beyond the cumulative review already assessed. However, the MAH was asked to submit this variation using a type II procedure. • After assessment of a PSUR, a MAH being asked by the EMA to add an adverse event to table 4.8, however, the MAH was required by EMA to submit this addition as a type II procedure to add the frequency of the event. • After assessment of a PSUR, a MAH was asked by the EMA to add a statement to the product information. The intended update was clear but the specific wording was not provided by EMA. Although the MAH agreed to this change and no additional data was required to support this update, it was asked to submit this variation using a type II procedure. • After CHMP assessment of a follow up measure (comprising a CSR), a MAH was required to delete a statement from the product information. This was submitted as a type IB procedure but was rejected by the EMA who reclassified the change as a type II procedure while no new data was submitted. It would be important to develop a harmonised and pragmatic approach for increasing the accessibility of the Type IB procedure that would allow all parties to focus resources on the procedures with most impact on public health. **Proposed change:**	

Variations reference	Stakeholder number ***(To be completed by the Agency)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		Revise the title: *Implementation of changes* **in the Summary of Product Characteristics, Labelling or Package Leaflet** *requested by the EMA/National Competent Authority following the assessment of an Urgent Safety Restriction, class labelling, a Periodic Safety Update report(*), Risk Management Plan, Post-Authorisation Measure/Specific Obligation, data submitted under Article 45/46 of Regulation (EC) No 1901/2006, or amendments to reflect a competent authority Core SPC.* Revise the note: *(*) This variation does not apply to implementation of changes* **for Centrally Authorised Products** *following the assessment of a Periodic Safety Update report carried out in accordance with procedures Art 107e to 107g of Directive 2001/83/EC and Art 28 of Regulation (EC) No 726/2004.* Revise the description: *a) Implementation of agreed wording change(s) for which no* **significant** *new additional data are submitted by the MAH* *b) Implementation of change(s) which require to be further substantiated by* **significant** *new additional data to be submitted by the MAH*	
C.I.4		**Comment:** The new note to variation C.I.4 indicates that this variation applies "*for the submission of results of studies performed in compliance with a Paediatric Investigation Plan which do not support a paediatric indication"*. To avoid confusion between variations and the routine submission of paediatric results under Article 46 of the Paediatric Regulation, the note should be clear that it applies to proposed changes to the product information arising from results of paediatric studies. **Proposed change:** Revise the note: *This variation applies also for* **modifications to the Summary of Product Characteristics to reflect** *the* ***~~submission of~~*** *results of studies performed in compliance with a Paediatric Investigation Plan which do not support a paediatric indication.*	M

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
C.I.8 a)		**Comment:** It is proposed that the introduction of a summary of the pharmacovigilance system be classified as a Type IA_{IN} procedure. A type IA_{IN} variation implies that the change must be made for all MAs within a very short timeframe following creation of the PSMF, which could be impractical for many MAHs. The EMA/HMA Q&A, clearly state that introduction of the PSMF ahead of the mandatory timelines is voluntary; the MAH should be allowed flexibility in choosing when to submit the variation, based on resources, budget or other practical considerations, particularly for MA where there is no DDPS currently included in the MA. The pharmacovigilance legislation foresees the possibility to introduce the summary as part of the renewal of the MA. It may be helpful, therefore, to indicate this in the note. **Proposed change:** Revise Procedure Type to **IA** Please add a note: **This variation covers the situation where the introduction of the PSMF summary is not done as part of another regulatory procedure (e.g. renewal).**	M
Note on Variation C.I.8 b)		**Comment:** We welcome and fully support the possibility, as described in this note, to make changes to the QPPV details and PSMF location in the Art.57 database only, without the need for a variation. It would be helpful if the Commission or EMA could clarify what is meant by the Art.57 database being functional, and give an indication of when this may occur.	C
Note on Variation C.I.9		**Comment:** DDPS should no longer be needed after 2 or 21 July 2015, as a PSMF should have been introduced for all products by those dates for centralised or nationally authorised products respectively. It may be helpful, therefore, to indicate this in the note. **Proposed change:** Amend the note	m

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		C.I.9 covers changes to an existing pharmacovigilance system 1) for veterinary medicinal products and 2) for human medicinal products during the transitional period until the first time introduction of a PSMF, **to be done latest by 2 July 2015(centrally authorised products) or 21 July 2015 (nationally authorised products.**	
C.I.10		**Comment:** Under the current draft proposal, there is overlap between variation categories C.I.10 "Changes to the conditions and/or obligations of the marketing authorisation due in particular to new quality, pre-clinical, clinical or pharmacovigilance data" and C.I.3 "Implementation of change(s) requested by the EMA/ National Competent Authority following the assessment of [...] Post-Authorisation Measure/Specific Obligation [...]". This overlap should be clarified in order to avoid multiple assessments of the same data package. Any discussion on necessary amendments of the Product Information should be conducted during the evaluation procedure and a separate variation fee should not be charged for the implementation of changes to the Product Information following the assessment of the new data. **Proposed change:** The titles and conditions of variation categories C.I.10 and C.I.3 should be reworded in order to avoid any overlap and multiple assessments of the same data package. **Comment:** It is acknowledged that changes to the conditions and /or obligations of the MA require careful evaluation. However, we assume that if changes to the conditions/obligations are requested by the relevant competent authority or are the result of previous assessment or considerations, some interaction already has taken place between the competent authority and the MAH. In this case it should be considered a Type IB, as limited assessment would be required. **Proposed change:** We strongly feel that the overlap brought by the introduction of variation C.I.10 would be detrimental for pharmaceutical companies who might end-up paying twice for the evaluation of the same data package, and suggest to introduce 2 categories:	C

Variations reference	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		a) Changes to the conditions and/or obligations of the marketing authorisation requested by/or agreed with the relevant competent authority Procedure Type: **IB** **b) Changes to the conditions and/or obligations of the marketing authorisation proposed by the Marketing Authorisation Holder** Procedure Type: **II**	
C.I.11		**Comment:** We welcome the clarification that no variation is required to align PSUR frequency/submission date with the list of Union reference dates in cases where the PSUR cycle is not specified in the MA. It would be even clearer, however, if this was addressed in the description of the variation, rather than the note. It is proposed to notify the change in the frequency with a Type IA_{IN}. We would like to highlight, that in GVP Module VII.C.3.7.(Amendment of the marketing authorisation according to the list of EU reference dates) it is stated that "*any changes to the dates and frequencies of submission of PSUR specified in the list take effect six months after the date of the publication on the European medicines web-portal. Where appropriate, marketing authorisation holders shall submit the relevant variation within these six months in order to reflect the new information in their marketing authorisations*". We propose to add a note to refer to the requirements in the GVP Module, and clarify expectation with regard to submission of this Type IA_{IN}. As part of the documentation item 1 to be submitted, it is stated, "*Attached to the cover letter of the variation application: A reference to the agreement reached by the CHMP/CMDh*" The list of Union reference dates will be publicly available on the European web-portal, we assume that a reference in the cover letter to this list should be sufficient. Please clarify. In addition, the documentation to be provided for variations to non-centralised products should be made clearer. **Proposed change:**	m

Variations reference	Stakeholder number ***(To be completed by the Agency)***	Comment and rationale; proposed changes ***(If changes to the wording are suggested, they should be highlighted using 'track changes')***	For information, indication of relative importance as Critical (C), Major (M), minor (m) or editorial (e) comment
		Revise the description of the variation: *C.I.11 Change in the frequency and/or date of submission of periodic safety update reports (PSUR)* **where specified in the marketing authorisation** Add a note: **Any changes to the dates and frequencies of submission of PSUR specified in the list take effect six months after the date of the publication on the European medicines web-portal. Where appropriate, marketing authorisation holders shall submit the relevant variation within these six months in order to reflect the new information in their marketing authorisations.** Revise the text in parentheses for documentation item 2 : *(For medicinal products authorised via the centralised procedure, the full set of annexes, including the revised Annex II should be provided~~)~~* **. For other products, the relevant revised MA documentation in the format required by the national competent authority should be used.)**	
C.I.12		**Comment:** As part of the documentation item 1 to be submitted, it is stated, "*Attached to the cover letter of the variation application: A reference to the list of medicinal products that are subject to additional monitoring"* *reached by the CHMP/CMDh*" The list of medicinal products that are subject to additional monitoring will be publicly available on the European web-portal, we assume that a reference in the cover letter to this list should be sufficient. There should be no requirement to submit a copy or paper documents, Please clarify.	m