IFAH-Europe contribution to the Commission public consultation paper:

'Review of the Variations Guideline'

IFAH-Europe has welcomed this consultation paper on the 'Review of the Variations Guidelines', as foreseen by Article 4(2) of Regulation 1234/2008[1]. Some of the changes proposed by the EU Variations Task Force do bring clarification, which was needed in some areas. We also note the introduction of new variations that we fear will counter the benefits gained from the Regulation towards reducing administrative burden. The following trend towards increased burden has especially been observed after two years' experience, and is unfortunately confirmed by some of the proposed changes. More generally:

- The classification GL is becoming lengthier, and consequently less user-friendly. Many variations have indeed been added (e.g. what could be handled as a single change under the previous framework is now split into several variations; also the increased level of information requested in dossiers lead to the introduction of more variations);
- Conditions to 'Do and Tell' Type IA variations are made more and more stringent, and counter the benefits from having introduced this concept of 'Do and Tell', which is becoming very difficult to comply with (e.g. B.I.a.4.c), B.I.b.1.d));
- The application of Article 5 for 'Unforeseen variations' is rather systematic, when the concept of default to Type IB should apply. Indeed, Article 5 should only be used in exceptional cases. Having to deal with unforeseen variations create additional workload on EMA and CMDv, and deviates resources from their main task.

We acknowledge that some of the key items raised by IFAH-Europe when responding to the public consultation in October 2011[2], and in a more recent paper dated 4th June 2012, have been addressed. Others, especially with regard to 'change of address in MRP/DCP' (A.1 – page 2) and 'changes to the DDPS' (C.II.7 – page 14) remain a major concern to our industry daily operations, and must be solved. IFAH-Europe proposes some solutions, which we urge the Commission to take on board. The table overleaf provides a more detailed input to the amended Guideline, which we hope will be carefully considered as part of the Commission commitment to achieve 'Better Regulation', while preserving animal and public health.

Finally, we wish to stress that it is unfortunate this consultation was initiated without prior indication as to when it was going to exactly take place; also the 1-month period was totally disproportionate to the size of the task. Thus, we had very little time to gain a full understanding of the proposed changes by the EU Task Force, which made it even more challenging to provide sound comments together with suitable solutions. For the next revision, we would welcome if a more transparent process was put in place. Also, we feel it would be a more valuable exercise if stakeholders were involved at an earlier stage in the work of the EU Variations Task Force. This way, a common understanding could be reached amongst all stakeholders, and would facilitate the final public consultation step.

In the meantime, a follow-up meeting with stakeholders on the outcome of this consultation, and prior to the public release of the revised GL, would be much welcomed.

[1] Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products – *Official Journal L 334, 12.12.2008, p. 7–24* http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:334:0007:0024:EN:PDF

[2] Outcome of the Commission 2011 public consultation on Variations http://ec.europa.eu/health/better-regulation-pc_2011_09_en.htm

Variation number	Currently proposed or revised change	Comment	IFAH-Europe proposal
A. Administrative changes			
A.1	Change in the name and/or address of the marketing authorisation holder (Type IA_{IN})	**Comment to the handling of the change**: in MRP/DCP, MAHs are currently asked to inform all the countries, even if the address changes only in one of them. This creates unnecessary burden on MAHs, and on agencies who receive information that is of no relevance to them. Thus, to notify such administrative changes, MAHs should be able to submit the information only to the country(ies) concerned with the change.	Add a note: **'For products registered via MRP/DCP, the MAH can notify only the country(ies) concerned with the change of address.'**
A.4	Change in the name and/or address of a manufacturer (including where relevant quality control testing sites), ASMF holder, or supplier of the active substance, starting material, reagent or intermediate used in the manufacture of the active substance (where specified in the product dossier) where no Ph. Eur. Certificate of Suitability is part of the approved dossier, or a manufacturer of a novel excipient	**Comment to the description of the change**: a 'novel' excipient is only considered as such at the time of registration; once variations are submitted, the excipient can no longer be qualified as 'novel', and the use of such terminology must be avoided. See also B.II.c.4 and 5.	Amend: 'Change in the name and/or address of a manufacturer … where no Ph. Eur. Certificate of Suitability is part of the approved dossier, or **of** a manufacturer of ~~a~~ **the** ~~novel~~ excipient **(when described in the dossier).**

Variation number	Currently proposed or revised change	Comment	IFAH-Europe proposal
B.I Quality changes to the active substance			
B.1.a.1	Change in the manufacturer of a starting material/reagent/Intermediate used in the manufacturing process of the active substance , or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. CoS is part of the approved dossier		
	g) Introduction of a new manufacturer of the active substance that is not supported by an ASMF and requires significant update to the relevant active substance section of the dossier (new Type II)	**Comment to the description of the change**: for consistency across the guideline, this variation should be described as done under B.II for finished product, i.e. 'Replacement or addition of a manufacturing site'. The same applies to 1.h), 1.i) and 1.k)	Amend g):' ~~Introduction~~ **Replacement or addition** of a ~~new~~ manufacturer of the active substance that is not supported by an ASMF… '
	h) Addition of an alternative sterilisation site for the active substance using a Ph.Eur. method (new Type IB) Documentation 8: 'Proof that the proposed site is appropriately authorised for the pharmaceutical form or product or manufacturing operation concerned, i.e.: For a manufacturing site within the EU/EEA: a … For a manufacturing site outside the EU/EEA: …'	See comment above on the description of the change. **Comment to the documentation**: this variation concerns the sterilization site for the active substance. Therefore, a declaration by the qualified person would be the most suitable document to supply.	Amend h): **Replacement or** addition of a~~n alternative~~ sterilisation site for the active substance using a Ph.Eur. method. Amend documentation 8: '**Declaration by the Qualified Person that the proposed site is appropriately authorised for the pharmaceutical form or product or manufacturing operation concerned**. ~~Proof that the proposed site is appropriately authorised for the pharmaceutical form or product or manufacturing operation concerned, i.e.: For a manufacturing site within the EU/EEA: a … / For a manufacturing site outside the EU/EEA: …~~'

Variation number	Currently proposed or revised change	Comment	IFAH-Europe proposal
B.1.a.1 *Continued from p. 3*	i) Introduction of a new site of micronisation (new Type IA)	See comment to g) above on the description of the change. Also, this change should cover other processes, and not be limited to 'micronisation'; thus, a more general wording should be introduced, e.g. 'physical processing'.	Amend i): '~~Introduction~~ **Replacement or addition** of a ~~new~~ site **for physical processing e.g. milling or** ~~of~~ micronisation.'
	k) New storage site of Master Cell Bank and/or Working Cell Banks (new Type IB)	See comment to g) above.	Amend k): '**Replacement or addition of a** ~~New~~ storage site of Master Cell Bank and/or Working Cell Banks.'
B.I.b.1	Change in the specification parameters and/or limits of an active substance / starting material/intermediate/reagent used in the manufacturing process of the active substance		
	h) 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 (Type IB)	**Comment to the classification for biologicals**: the exclusion of biologicals from a Type IB is not justified.	Amend h): '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.'
B.I.d.1	Change in the re-test period/storage period or storage conditions of the active substance where no Ph. Eur. CoS covering the re-test period of part of the dossier c) Change to an approved stability protocol (new Type IA)	**Question to the description of the change**: the scope of this type of change and condition 2 are not clear. Does it mean "approved" in terms of available stability guidelines? Some clarification would be helpful.	-

Variation number	Currently proposed or revised change	Comment	IFAH-Europe proposal
B.II Quality changes to the finished product			
B.II.a.3	Changes in composition (excipients) of the finished product		
	a) Changes in component of the flavoring or colouring system		
	1. Addition, deletion or replacement (Type IA_{IN}) 2. Increase or reduction (Type IA) Condition 11: For veterinary medicinal products for oral use, the change does not affect the uptake by target animal species	**Comment to condition 11**: in many veterinary dossiers, information concerning the uptake of the veterinary medicinal product may not be available. Therefore, it is impossible to prove that the colouring or flavoring agent is important for the uptake by the target animal species.	Amend condition 11: 'For veterinary medicinal products for oral use, the change does not **adversely affect** the uptake by target animal species**, and only when described in the dossier**.'
	3. Veterinary medicinal products for oral use for which the colouring or flavouring agent is important for the uptake by target animal species (Type II)	**Comment to the classification of the change**: a Type II is totally unjustified; this change should be deleted to allow a default to Type IB, when condition 11 to 1. and 2. (above) is not met.	Delete Variation 3.
B.II.b.2	Change to importer, batch release or arrangements and quality control testing of the finished product		
	c) Replacement or addition of a manufacturer responsible for importation and/or batch release: 2. Including batch control/testing (new Type II)	**Comment to the classification**: this variation is a Type IA_{IN} in the current classification guideline; the change to a Type II (which could just be a typo) is totally unjustified, as also demonstrated by the list of conditions to have to comply with.	Amend the classification to a Type IA_{IN}.
B.II.b.3	Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of the finished product		
		Minor changes to sterile products are not addressed, and could be covered by the existing variation f) for 'Minor change in the manufacturing process of an aqueous oral suspension'. The same documentation would apply.	Amend f) to read: 'Minor change in the manufacturing process of an aqueous oral suspension**, or of any sterile product**.'

Variation number	**Currently proposed or revised change**	**Comment**	**IFAH-Europe proposal**
B.II.c.3	Change in source of an excipient or reagent with TSE risk	Comment to the description of the change: In Directive 2009/9/EC, the term 'reagent' refers to laboratory reagents used for tests, and which have no contact with the product itself; in the Directive, the term 'starting material' also includes 'culture medium'. Thus, we feel it would be more appropriate to replace the term 'reagent' with 'starting material'. This way, the change could also cover, for example, the replacement of a classical culture medium by an animal component free (ACF) culture medium for the production of the active component (virus or bacterium).	Amend 3: 'Change in source of an excipient or ~~reagent~~ **starting material** with TSE risk to...' Also replace 'reagent' with 'starting material' in all relevant sub-sections of B.II.c.3.
B.II.c.4	Change in synthesis or recovery of a non pharmacopoeial excipient (when described in the dossier) or a novel excipient (Type IA)	**Comment to the description of the change**: as raised under A.4, a 'novel' excipient is only considered as such at the time of registration; once variations are submitted the excipient can no longer be qualified as 'novel', and the use of such terminology must be avoided.	Amend: B.II.c.4: 'Change in synthesis or recovery of a non pharmacopoeial excipient (when described in the dossier) ~~or a novel excipient~~' B.II.c.5: 'Change in manufacturer of **an** ~~novel~~ excipient'; sub-sections a), b) and c) should also be amended accordingly.
B.II.c.5	Change in manufacturer of a novel excipient		

Variation number	**Currently proposed or revised change**	**Comment**	**IFAH-Europe proposal**
B.II.d.1	Change in the specification parameters and/or limits of the finished product		
	a) Tightening of specifications limits of the finished product (Type IA) The same applies to all the other following quality changes: - Active substance: B.I.a.4.a, B.I.b.1.a and B.I.c.2.a - Finished product: B.II.b.5.a, B.II.c.1.a and B.II.e.2.a - Medical devices: B.IV.2.a	**Comment to the classification**: these changes are Type IA unless condition 1 "the change is not a consequence of any commitment from previous assessments to review specification limits (e.g. made during the procedure for the MA application or a Type II variation procedure)" is not fulfilled, in which case you would expect it to default to Type IB, though this is questionable. Also in practice, a Type II has been requested, which is totally unjustified. Thus, we suggest introducing a new variation to cover all cases where data have already been assessed and in which case a Type IA should apply.	Add a **new Type IA** variation for: '**Implementation of changes following follow-up measures for which data have already been assessed and approved.**'
	g) Addition or replacement (excluding biological or immunological product) of a specification parameter, with its corresponding test method, as a result of a safety or quality issue (Type IB)	**Comment to the classification for biologicals**: the exclusion of biologicals from a Type IB is not justified.	Amend g): 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.

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B.II.d.1 *Continued from p.7*	h) Update of the dossier to comply with the provisions of an updated general monograph of the Ph. Eur for the finished product (new Type IA_{IN}) Condition 8: If the change concerns the updating of the microbial control limits to be in line with the current Pharmacopoeia, and the currently registered microbial control limits (present situation) are totally in line with the pre January 2008 (non harmonised) situation and does not include any additional specified controls over and above the Pharmacopoeia requirements for the particular dosage form and the proposed controls are totally in line with the harmonised monograph.	**Comment to the location of the change**: variations in relation to monographs of the Eur. Ph. should all appear under B.III. **Comment to condition 8**: the wording of this condition is very unclear and must be reworded.	Move B.II.d.1.h) to B.III.2, where a sub-section d) should be added. Clarify the wording of condition 8.
	i) Ph. Eur. 2.9.40 Uniformity of dosage units is introduced to replace the currently registered method, either Ph. Eur. 2.9.5 (Uniformity of mass) or Ph. Eur. 2.9.6 (Uniformity of content)" is a very specific case, where we do not see the need to have this classification in the guideline (new Type IB)	**Comment to the change**: such a change would fall under change B.II.d.1.g): 'replacement of a specification parameter, with its corresponding test method'; adding another variation seems superfluous and adds to the complexity of the GL.	Delete this change.
B.II.d.2	Change in test procedure for the finished product		
	f) To reflect compliance with the Ph. Eur. and remove reference to the internal test method and test method number (new Type IA)	**Comment to the location of the change**: variations in relation to monographs of the Eur. Ph. should all appear under B.III.	Move B.II.d.2. f) to B.III.2, where a sub-section e) should be added.
B.II.f.1	Change in the shelf-life or storage conditions of the finished product		
	e) Change to an approved stability protocol (new Type IA)	**Question on the description of the change**: the scope of this type of change and condition 2 are not clear. Does it mean "approved" in terms of available stability guidelines? Some clarification would be helpful.	-

Variation number	Currently proposed or revised change	Comment	IFAH-Europe proposal
B.II.i.1	Update to the "Adventitious Agents Safety Evaluation" information (section 3.2.A.2)	**Comment to the scope of the change**: reference is made to 3.2.A.2 which is a CTD section; reference to the NtA appears to be missing. Also for consistency, we suggest adding the term 'extraneous'.	Amend the wording by adding a reference to the NtA and the word 'extraneous' as follows: 'adventitious**/extraneous**.'
Joint comments to B.I and B.II			
B.I.a.4.f B.I.b.1.h B.I.c.2.d B.II.b.5.f B.II.c.1.f B.II.d.1.g B.II.e.2.d B.IV.2.e	These changes concern the addition or replacement of a test, parameter or limit as a result of a safety or quality issue, and are classified as a Type IB.	**Comment to the classification of the change and its condition**: we propose to classify these changes as Type IA_{IN} to the condition that the change is not the result of a safety or quality issue, in which case the change would default to Type IB as it is currently described.	Amend the classification from a Type IB to a **Type IA_{IN}** with one additional condition for each, as follows: '**The change is not the result of a safety or quality issue**'.
B.I.a.4.c) B.I.b.1.d) B.II.b.5.c) B.II.d.1.d)	These changes relate to the deletion of 'non-significant test or parameters' where a new condition has been added in all cases: 'The specification parameter does not concern a critical parameter, for example any of the following: assay, impurities (unless a particular solvent is definitely not used in the manufacture of the active substance), any critical physical characteristics e.g. particle size, bulk or tapped density, identity test, water, any request for skip testing.	**Comment to the condition**: condition 7 has been added and appears to be unnecessary. Indeed, it is the MAH responsibility to demonstrate the non-significance of a process. Thus, such condition is totally unnecessary, and only makes the system even more stringent; also it is countered to achieving simplification.	Delete: the relevant conditions in each of these variations (i.e. condition 7, condition 8, condition 7 and condition 9)

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B.III CEPs/TSE/Monographs: this section brings in a whole new load of new Type IA variations for the 'deletion of certificates', and which IFAH-Europe is challenging.			
B.III.1	Submission of a new or updated Ph. Eur. Certificate of suitability or deletion of Ph. Eur. certificate of suitability for an active substance, a starting material/reagent/intermediate used in the manufacturing process of the active substance, or for an excipient		
	a) European Pharmacopoeial Certificate of Suitability to the relevant Ph. Eur. Monograph		
	5. Deletion of certificates (in case multiple certificates exist per material) (new Type IA)	**Comment to the variation**: such new change will significantly increase the administrative burden and create an unnecessary congestion of the regulatory system, and of its resources. Also where condition 10 is met, i.e. 'at least one manufacturer for the same substance remains in the dossier', such change appears totally unnecessary. The same comment applies to b) 4 (overleaf).	Delete this new variation 5.
	6. New certificate for a non-sterile active substance that is to be used in a sterile medicinal product, where water is used in the last steps of the synthesis and the material is not claimed to be endotoxin free (new Type IB) Documentation 6: suitable evidence to confirm that the water used in the final steps of the synthesis of the active substance complies with NfG on quality of water for pharmaceutical use (CPMP/QWP/158/01 Rev or EMEA/CVMP/115/01 Rev)	**Comment to the change:** to ensure simplification, and allow application of the default to Type IB concept, we suggest amending condition 11 to Variations 1. and 3., in which case the variation described under 6. no longer needs to be introduced. **Comment to the documentation**: according to Ph. Eur., parenteral preparations for veterinary use can in some cases justify an exemption to bacterial endotoxin test (Ph. Eur. monograph no. 520). In this case, or other cases where justified, documentation 6 is not applicable.	Delete Variation 6., and amend condition 11 and documentation 6 as follows: Condition 11: 'If the active substance is not sterile and to be used in a sterile medicinal product, then (according to the CEP), it must not use water during the last steps of the synthesis. If it does, the active substance must be claimed to be free from bacterial endotoxins **or the exemption of the bacterial endotoxin test must be justified"** Documentation 6: 'Suitable evidence to confirm that the water used in the final steps of the synthesis of the active substance complies with NfG on quality of water for pharmaceutical use (CPMP/QWP/158/01 Rev or EMEA/CVMP/115/01 Rev), **where applicable**.'

Variation number	**Currently proposed or revised change**	**Comment**	**IFAH-Europe proposal**
B.III.1	Submission of a new or updated Ph. Eur. Certificate of suitability or deletion of Ph. Eur. certificate of suitability for an active substance, a starting material/reagent/intermediate used in the manufacturing process of the active substance, or for an excipient		
	b) European Pharmacopoeial TSE Certificate of suitability for an active substance/starting material/reagent/ intermediate/or excipient		
	1. New certificate for an active substance from a new or an already approved manufacturer	**Comment to the conditions**: Condition 3 should be amended to cover for the situation where absence of viral risk has been demonstrated by e.g. inactivation. Condition 9 appears to be superfluous here, and should be deleted.	Amend condition 3 And delete condition 9. Condition 3: "The manufacturing process of the active substance, starting material /reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required, **unless the absence of viral risk (e.g. inactivation) is demonstrated**."
	2. New certificate for a starting material/reagent/ intermediate/or excipient from a new or an already approved manufacturer (Type IA) Condition 3: the manufacturing process of the active substance, starting material/reagent/intermediate does not include the use of materials of human or animal origin for which an assessment of viral safety data is required. Condition 9: If Gelatin is to be used in a medicinal product that is for parenteral use, if manufactured from bones, it should only be manufactured in compliance country requirements as stated in the Note for Guidance for minimising the risk transmitting animal spongiform encephalopathy (EMA/410/01 current revision).		
	4. Deletion of certificates (in case multiple certificates exist per material) (new Type IA).	**Comment to the variation** (same as a) 5): such new change will significantly increase the administrative burden and create an unnecessary congestion of the regulatory system and of its resources. Also where condition 10 is met, i.e. 'at least one manufacturer for the same substance remains in the dossier', such change appears totally unnecessary.	Delete this new variation 4

B.III.1.b) *Continued from p. 11*	5. New/updated certificate from an already approved/new manufacturer using materials of human or animal origin for which an assessment of the risk with respect to potential contamination with adventitious agents is required (new Type II)	**Comment to the variation**: this newly introduced change infringes with the already existing b) 2 for new certificates (above), in which case, if condition 3 cannot be met and a viral risk assessment is necessary, the change should default to a Type IB. For an updated certificate, B.III.1.b)3 applies; to cover for the situation where a viral risk assessment is necessary, condition 3 could be added to this change.	Delete this new variation 5 and add condition 3 to: B.III.1.b)3.

Not listed	
Once a product has been authorised and produced for several years, the manufacturing process and/or testing procedures/specifications drift away from those described in the dossier. They are often just slight modifications to the process/testing without significant impact on the quality, safety or efficacy of the product; this nonetheless means that the processes have deviated from those described in the dossier, in which case MAHs are expected to draw an extensive list of all the changes, which is often not possible. On the other hand, the introduction of a new Type II variation to include all these changes should be considered, to ensure an appropriate assessment of the proposed changes, while removing the complexity for both authorities and industry to try and list each single change. Also the January/February 2012 CMDv press release indicates that some MSs do accept this umbrella concept for MA transfer. Thus, it should be considered for introduction in the Commission classification guideline.	Add a new Type II variation: **'Update of the quality Part 2 of the dossier with several changes, without significant impact on quality, safety or efficacy**.

Variation number	Currently proposed or revised change	Comment	IFAH-Europe proposal
C. Safety, Efficacy, Pharmacovigilance changes			
C.I.1	Documentations 1 and 2	**Comment to documentations 1 and 2**: these refer to CMDh agreement only; a reference to CMDv should be added.	Amend documentations 1 and 2: "… or the agreement reached by CMDh **or CMDv** (where applicable)…"
C.I.2	Change in the SPC labeling or package leaflet of a generic/hybrid/biosimilar medicinal product following the assessment of the same change for the reference product: a) For which no additional data are submitted (Type IB).	**Comment to the scope of the change**: the same should apply to changes to the SPC of an informed consent dossier, where the change has already been evaluated and approved for the reference product. In such case, a Type II has been requested in the past, whereas the generic dossier benefits from the same change (a new claim in that instance) via a Type IB 30 days procedure, which seems totally disproportionate. Similarly, this variation should also cover changes to the SPC or package leaflet of the reference product to follow the information of the generic.	Amend C.I.2: 'Change in the SPC labeling or package leaflet of a generic/hybrid/biosimilar medicinal product **or informed consent** following the assessment of the same change for the reference product, **and vice versa**.'
C.I.3.a	Implementation of agreed wording change(s) for which no new additional data are submitted by the MAH (Type IB)	**Comment to the classification**: if the wording has been agreed upon, no assessment is necessary and a Type IA variation should be sufficient.	Amend the classification to a 'Type IA'
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 (new Type II) *Note: this variation covers the situation where the only change introduced concerns the conditions and/or obligations of the marketing authorisation, including the conditions and/or obligations of marketing authorisations under exceptional circumstances and conditional marketing authorisation*	**Question on the scope of the change**: the scope of this classification is not clear. How is the term "*changes*" defined? Addition, deletion or otherwise? Usually such actions take place after assessment of data submitted by the MAH to fulfill conditions/obligations. Does it mean that a change to the list of outstanding conditions/obligations needs another variation in which another assessment takes place?	Clarification on the purpose of this newly introduced change would be welcomed.

Variation number	Currently proposed or revised change	Comment	IFAH-Europe proposal
C.II.7	C.II.7 Introduction of a new Pharmacovigilance system a) Which has not been assessed by the relevant national competent authority/EMA for another product of the same MAH (Type II) b) Which has been assessed by the relevant national competent authority/EMA for another product of the same MAH(*) (Type IB)	**Comment to the description of the change and its classification**: the DDPS[3] is a document that describes the MAH pharmacovigilance system, i.e. it is a company, and not a product specific document. Nevertheless, MAHs currently have to submit the DDPS together with each MA application, whatever the registration route. Thus, the DDPS becomes part of all dossiers, which have to be subsequently amended when changes to the DDPS occur. For example, a change of the QPPV details (current C.I.9.b) entails the submission of this change to each competent authority and for each single marketing authorisation; the latter can be facilitated by the use of the 'grouping' procedure, where accepted by all member states, which currently is not the case. This generates huge administrative burden and totally disproportionate cost for such minor administrative changes that require no assessment. For instance, the cost of a Type IA variation C.I.9.b for 10 centrally authorised products would amount to a total of €29,000 [10xType IA fee of €2,900]. This is just the cost of notifying EMA, while the same exercise has to be carried out with each national competent authority. Thus, the financial consequences are highly significant when a MAH can have several hundred authorisations across Europe. Also, in the current climate of companies' mergers and products' transfers, such changes are likely to occur even more frequently, and such cost is totally disproportionate. Thus, and pending the introduction of a legal basis for the concept of pharmacovigilance system master file, the classification must be reviewed to allow the introduction of a new system, or any changes to an existing one, to be submitted as a Type IA, where **a single Type IA notification is valid for all MAs of a same competent authority**. This notification approach will prepare the ground for the next step, i.e. the introduction of the master file concept, whereby the description of the system will be available for evaluation upon request or at inspection.	Amend C.II.7:' Introduction of a new pharmacovigilance system **or changes to an existing system**.' - Type IA_{IN} ***Note: a single Type IA notification can cover all the marketing authorisations***

[3] DDPS: Detailed Description of the Pharmacovigilance System

Other (minor) comments, including typos

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 biological / immunological / immunochemical methods takes place	The sentence does not read very well	Changes to quality control testing arrangements for a biological active substance~~-~~; or replacement or addition of a site where batch control/testing including a biological / immunological / immunochemical methods takes place
B.I.a.2	Documentation 5: 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	'that' is repeated twice	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.I.f.4.b)	The implementation of the change requires no further supportive and should be notified to the competent authorities within 12 months of implementation	The word 'data' is missing	The implementation of the change requires no further supportive data and should be notified to the competent authorities within 12 months of implementation.