EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

12 July 2012

Submission of comments on Review of the Variations Guidelines (EC 1234/2008)

Comments from:

Name of organisation or individual
Leem

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).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	It is proposed to add the notion of Intermediate of Production for the Finished Product in the DP part. With the current version of the Variations Guidelines, there are potential difficulties to determine the appropriate variation number between DS and DP for Intermediate of Production manufactured from DS and used for manufacture of DP.	
	It is proposed to add a note to clarify the notion of Novel Excipient in the Variations Guidelines. Notion of Novel Excipient was introduced for new registration and for Marketing Authorization dossier. After some time, and thus when the present document applies, the excipient could not be anymore considered as a novel excipient. As a general rules, it is proposed to consider a Novel Excipient as novel up to the first renewal.	
	With this revision the terms “significant change” or “substantial change” were introduced. It is not clear if these terms cover the same notions than the term “major change” used in current description. If it is the case, it is proposed to replace the term “significant change” or “substantial change” by “major change” for harmonization with other parts of the document.	

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	All variation type adopted via Article 5 seem not appear in the new version of this variation guideline EC1234/2008.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	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')*	Outcome *(To be completed by the Agency)*
A4 (change in the name and/or address of a Manufacturer)		Comment: After some time, and thus when the present document applies, the excipient could not be anymore considered as a novel excipient. As a general rules, it is proposed here to consider a Novel Excipient as novel up to the first renewal. Proposed change (if any): It is proposed to add a note to indicate when an excipient submitted as a novel excipient in the initial registration dossier is considered as a novel excipient, and thus when this change applies (novel excipient) or not (excipient). E.g. "Excipient submitted as a Novel Excipient in the Marketing Authorisation dossier must still be considered as a novel excipient before the first renewal and in this case change must be submitted for this excipient as above described.").	
Change B.I.a.1 (Change in the manufacturing process of materials for the active substance)		Comment: The case where this is no ASMF and no significant update is not listed here. It is therefore our understanding that a change in the manufacturing process of the drug substance with no significant update to the dossier when this drug substance is not covered by an ASMF is a change type IB.	

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		Proposed change (if any): for clarification, it is proposed to add a line for change in the manufacturing process of the drug substance with no significant update to the dossier when this drug substance is not covered by an ASMF and to specifically list this change as IB.	
Change B.I.a.2 (Change in the manufacturing process of the active substance)		For change type c: Comment: It is not clear what is referred as "protocol". Protocol can be understood as clinical protocol, comparability protocol, Post Approval Change Management Protocol, etc… Proposed change (if any): Clarification of which type of protocol is considered when it is mentioned "… and is not related to a protocol".	
Change B.I.a.2 (Change in the manufacturing process of the active substance)		For change type f Comment: For products not initially developed with an enhanced approach, a change can be supported by an enhanced approach. It is thus proposed to have this category of change for enhanced approach for both initial development or post-approval change. Proposed change (if any): addition of the term "and/or". Proposed sentence is "Change to non critical processes parameters where the process has been developed and/or optimised using an enhanced development approach". Condition 8 becomes "the manufacturing process has been	

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		developed and/or optimized using and enhanced development approach…".	
Change B.I.a.2 (Change in the manufacturing process of the active substance)		Comment: For Documentation 5, it is not clear what kind of document can be accepted as "Documentary evidence that the non criticality of the parameter has been accepted". Proposed change (if any): To provide examples of documentary evidence that can be accepted to support this change. Typo in the current sentence (word "that" indicated twice).	
Change B.I.a.4 (Change to in-process test or limits of the active substance)		For change type c Comment: the term "significant change" was introduced. It is not clear if the term "significant change" covers the same notions than the term "major change" used in current description. Proposed change (if any): replacement of the term "significant change" by "major change" for harmonization with other parts of the document.	
Change B.I.a.4 (Change to in-process test or limits of the active substance)		For change type f Comment: For products not initially developed with an enhanced approach, a change can be supported by an enhanced approach. It is thus proposed to have this category of change for enhanced approach for both initial development	

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		or post-approval change. Proposed change (if any): addition of the term "and/or". Proposed sentence is "Change to the limits of non critical processes parameters where the process has been developed and/or optimised using an enhanced development approach". Condition 8 becomes "the manufacturing process has been developed and or/optimized using and enhanced development approach…".	
Change B.I.a.4 (Change to in-process test or limits of the active substance)		Comment: For Documentation 7, it is not clear what kind of document can be accepted as "Documentary evidence that the non criticality of the parameter has been accepted". Proposed change (if any): To provide examples of documentary evidence that can be accepted to support this change. Typo in the current sentence (word "that" indicated twice).	
Change B.I.b.1 (specifications DS part)		For change d: Comment: odour is provided as an example of an obsolete parameter. This example is seen as not necessary representative of current requests for deletion of obsolete parameters and is therefore not proposed to provide this example. Proposed change (if any): It is proposed to remove "odour" as	

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		proposed example.	
Change B.I.b.1 (specifications DS part)		For change h: Comment: Biological and immunological substances are excluded from this category, type IB, and thus are categorized per default, i.e. under IB. This category can thus cover both biological/immunological products and none biological/immunological products, with the same requirements and both under IB. Proposed change (if any): "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"	
Change B.I.e.1 (Introduction of a new Design Space DS)		Comment: For ease of use, possibility to have only one category as documentation to be supplied and as procedure type are the same for both sub-categories (i.e. Design Space =Type II). Proposed change (if any): merging of the two sub-categories into one category indicating that the submission of a Design Space is a Type II.	
Change B.I.f.4 (implementation further to post-		For change a and b: Comment: There is no difference in the description of the change, in the conditions to be fulfilled and in the	

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approval Change Management Protocol)		documentation to be supplied for changes a and b, respectively as IA_{IN} and IA. The implementation of the change foreseen in an approved change management protocol and requiring no further supportive data can therefore be either submitted immediately under IA_{IN} or within 12 months under IA. Proposed change (if any): for clarification, it is proposed to delete change a (type IA_{IN}) and list this change only as b (type IA). Elements can also be provided immediately (i.e. as IA_{IN}) under IA, i.e. within 12 month, if wanted. In the description for change b the word "data" is missing ("… and requires no further supportive data…").	
Change B.I.f.4 (implementation further to post-approval Change Management Protocol)		For Documentation 2: Comment: a "*" is indicated. It seems it relates to the notes for change B.I.f.4. Proposed change (if any): for clarification, it is proposed to add a "*" to the note, i.e. "* Note: Minor changes to a protocol to reflect…".	
Change B.II.b.1 (manufacturing site finished product)		Comment: Typo in the list for Documentation for change b (",,"). Proposed change (if any): 1, 2, 3, 4, 8, 9. For change c : could a "complex" manufacturing process be explained ?	

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Change B.II.b.2 (importer, batch release & QC)		Comment: It is not clear what the word "importer" refers to (i.e. a Marketing Authorization Holder who import the drug product, the company in charge of importation operations, the storage of imported drugs, parallel import, etc..). Proposed change (if any): to clarify what is referred as importer.	
Change B.II.b.2 (importer, batch release & QC)		For change c2: Comment: It is not clear why this change was upgraded from IA_{IN} to II. If all the required conditions are fulfilled (GMP Certificate, etc..) it seems there is no reason to upgrade from IA_{IN}. Proposed change (if any): to keep the category IA_{IN} for change c2 (provided that all the required conditions are fulfilled).	
Change B.II.b.2 (importer, batch release & QC)		For change c3: Comment: All conditions to be fulfilled for change C2 (batch control testing for a non biological product) applies to change c3 (batch control testing for a biological product). It is therefore proposed to add the conditions of c2 to c3 and thus as c2 and c3 will share the same description of the change (batch control testing), same conditions to be fulfilled and same documentation to be provided, it is proposed to have in a single category, under type II, batch control testing, either	

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		for a non biological product or a biological product. Proposed change (if any): Deletion of Change c3 and deletion of Condition 3 in change B.II.b.2 to have all batch control testing as Type II.	
Change B.II.b.3 (Change in the manufacturing process of the finished product)		For change type g: Same comment as for the Drug Substance. Comment: For products not initially developed with an enhanced approach, a change can be supported by an enhanced approach. It is thus proposed to have this category of change for enhanced approach for both initial development or post-approval change. Proposed change (if any): addition of the term "and/or". Proposed sentence is "Change to non critical process parameters where the process has been developed and/or optimised using an enhanced development approach". Condition 8 becomes "the manufacturing process has been developed and/or optimized using and enhanced development approach…".	
Change B.II.b.3 (Change in the manufacturing process of the finished product)		Comment: For Documentation 5, it is not clear what kind of document can be accepted as "Documentary evidence that the non criticality of the parameter has been accepted". Proposed change (if any): To provide examples of	

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		documentary evidence that can be accepted to support this change. Typo in the current sentence (word "that" indicated twice).	
Change B.II.b.5 (Change to in-process test or limits of the finished product)		For change type g: Same comment as for the Drug Substance. Comment: For products not initially developed with an enhanced approach, a change can be supported by an enhanced approach. It is thus proposed to have this category of change for enhanced approach for both initial development or post-approval change. Proposed change (if any): addition of the term "and/or". Proposed sentence is "Change to the limits of non critical processes parameters where the process has been developed and/or optimised using an enhanced development approach". Condition 8 becomes "the manufacturing process has been developed and or/optimized using and enhanced development approach…".	
Change B.II.b.5 (Change to in-process test or limits of the finished product)		Comment: For Documentation 8, it is not clear what kind of document can be accepted as "Documentary evidence that the non criticality of the parameter has been accepted". Proposed change (if any): To provide examples of documentary evidence that can be accepted to support this change.	

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		Typo in the current sentence (word "that" indicated twice).	
Change B.II.c.2 (test procedure for an excipient)		Comment: The term "substantial change" was introduced. It is not clear if this term covers the same notions than the term "major change" used in current other parts. Proposed change (if any): it is proposed to replace the term "significant change" by "major change" for harmonization with other parts of the document.	
Change B.II.c.4 (excipient)		Same comment as for A4. Comment: After some time, and thus when the present guidelines apply, the excipient could not be anymore considered as a novel excipient. As a general rules, it is proposed here to consider a Novel Excipient as novel up to the first renewal. Proposed change (if any): It is proposed to add a note to indicate when an excipient submitted as a novel excipient in the initial registration dossier is considered no more as a novel excipient, and thus when this change applies (novel excipient) or not (excipient). E.g. "Excipient submitted as a Novel Excipient in the Marketing Authorisation dossier must still be considered as a novel excipient before the first renewal and in this case present change must be submitted for this excipient as above described").	

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Change B.II.c.5 (manufacturer excipient)		Sale comment as B.II.c.4 (novel excipient) plus: Comment: The Application Form is not listed in Documentation. Proposed change (if any): Add the Application Form to provide in 2.5 in Documentation.	
Change B.II.d.1 (change in specification parameter for finished product)		For change h & i: Comment: compliance with a monograph of the Ph.Eur. is compulsory and change must be implemented within 6 months after the publication of the monograph. Dossier requirement is "complies with current Ph. Eur. Monograph" and the publication of a new monograph may lead to changes to comply with the new monograph but does not trigger the submission of a variation. In the same way, the Ph. Eur. 2.9.40 to replace 2.9.5 is linked to a specific change in the Ph. Eur. and our understanding is that such a specific change, at a specific time, should not be listed in a general document such as the variation guidelines. We understand that if a change to comply with a new monograph involves a change in the Certificate of Analysis, this information must be notified by the Marketing Authorization Holder to the relevant Health Authorities (e.g. for batch release testing organizations) but not necessarily through a variation process.	

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		Proposed change (if any): It is proposed to delete changes h and i.	
Change B.II.d.2 (test procedure for finished product)		For change c: Comment: It is not clear what is referred as "protocol". Protocol can be understood as clinical protocol, comparability protocol, Post Approval Change Management Protocol, etc… Proposed change (if any): Clarification of which type of protocol is considered when mentioned "and is not related to a protocol". As indicated before, it is also proposed to replace the wording "substantial change" by "major change".	
Change B.II.d.2 (test procedure for finished product)		For change e: Comment: In the case of a test procedure from Ph. Eur., the dossier mentions "complies with Ph. Eur. method/monograph xxx". The publication of a new method or monograph may lead to changes to comply with the new method or monograph but does not trigger the submission of a variation. Proposed change (if any): It is proposed to delete change e.	
Change B.II.d.2 (test procedure for finished product)		For change f: Comment: This change is for the replacement of an internal test method by a Ph. Eur. test method and list Condition 5 "the registered test procedure already refers to the general monograph of the Ph. Eur. …" as a condition to be fulfilled.	

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		Proposed change (if any): Deletion of Condition 5 in the list of condition to be fulfilled (and thus deletion of Condition 5 in the list of conditions as only applicable for Change e and as it was previously proposed to delete Change e).	
Change B.II.g.1 (introduction of a new Design Space DP)		Comment: For ease of use, possibility to have only one category as documentation to be supplied and as procedure type are the same for both sub-categories (i.e. Design Space =Type II). Proposed change (if any): merging of the two sub-categories into one category indicating that the submission of a Design Space is a Type II.	
Change B.II.h.4 (introduction of a new Design Space DP)		For change a and b: Same comment as for the DS Comment: There is no difference in the description of the change, in the conditions to be fulfilled and in the documentation to be supplied for changes a and b, respectively as IA_{IN} and IA. The implementation of the change foreseen in an approved change management protocol and requiring no further supportive data can therefore be either submitted immediately under IA_{IN} or within 12 months under IA. Proposed change (if any): for clarification, it is proposed to	

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		delete change a (type IA_{IN}) and list this change only as b (type IA). Elements can also be provided immediately (i.e. as IA_{IN}) under IA, i.e. within 12 month, if wanted. In the description for change b the word "data" is missing ("… and requires no further supportive data…").	
Change B.II.h.4 (introduction of a new Design Space DP)		For change d: Comment: Biological and immunological medicinal products are specific products and require specific Post-Approval Management Protocol, with specific approach and specific studies. However, once the specific approach is reviewed and approved with the Post-Approval Management Protocol it is proposed to have the same approach for implementation of a change for biological products than for non-biological products. If the studies were performed in accordance with the Post-Approval Management Protocol and if the results complies with the acceptance criteria provided in the Post-Approval Management Protocol, there is no reason to consider a Post Approval Management Protocol for a biological product different than for a non Biological Product. Proposed change (if any): It is proposed to delete change d and keep only a change a for implementation of a change not requiring further data (IA) and a change b for implementation of a change requiring further data (IB). Documentation 5, created specifically for change d, can thus be deleted from the list of documentation.	

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B.III.1 (CEP)		Comment: Certificates of Suitability are issued by EDQM further to the assessment of compliance with Ph. Eur requirements. The assessment is thus already performed by EDQM and no variation should be required for a new version of a Certificate of Suitability provided in a dossier if the new version is not linked to a change. It is therefore proposed to have the change B.III.1 to provide guidance for addition of new Certificate, for deletion of Certificate or for new version of Certificate if associated to a change. For workload burden reduction it is not proposed to submit new version of Certificates if not associated to a change. Proposed change (if any): It is proposed to delete changes a2 (updated certificate with no new site) and b3 (updated certificate from an already manufacturing site). Deletion of notion of updated certificate in the scope of the B.III.1, i.e. update of Certificates not triggering variations and not update if Certificated not listed here and thus triggering type IB. Proposed general description is "B.III.1 Submission of a new ~~or updated~~ Ph. Eur. Certificate of Suitability or deletion of Ph. Eur. Certificate of Suitability".	
C.I.1 (Change in SmPC, labeling and packaging)		Comment: It is not proposed to include PASS and PSUR procedures in this variation. Proposed change (if any): It is proposed to delete the references associated to PASS and PSUR Procedures.	

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Please add more rows if needed.