July 12, 2012

Submission of Suggestions on Public Consultation Paper – Review of the Variations Guidelines

Contribution from:

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Variation number/ Condition number/ Documentation number	Variation title/Condition/ Documentation	Comment and rationale; proposed changes
A.4	Change in the name and/or address of the 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 the novel excipients.	**Comment and rationale**: In some instances, the supplier of solvents is also specified in the dossier. This variation category should, therefore, take into account the change in name/address of supplier of solvents **Proposed change (if any)**: Change in the name and/or address of the manufacturer (including where relevant quality control testing sites), ASMF holder or supplier of the active substance, starting material, reagent, solvent 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 the novel excipients.
A.5.b	All other (including supplier of packaging components or devices (where specified in the dossier))	**Comment and rationale**: In some instances, the supplier of excipients is also specified in the dossier. This variation category should, therefore, take into account the change in name/address of supplier of excipients **Proposed change (if any)**: All other (including supplier of excipients, packaging components or devices (where specified in the dossier))
B.I.a.1.b and B.I.a.1.g	Introduction of a manufacturer of the active substance supported by an ASMF and 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	**Comment and rationale**: The reason for the deletion of word "new" from B.I.a.1.b is not clear. In case of any valid reason, the word "new" should also be deleted from B.I.a.1.g to maintain uniformity. **Proposed change (if any)**: B.I.a.1.g Introduction of a manufacturer of the active substance not supported by an ASMF and requires significant update to the relevant active substance section of the dossier.

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B.I.a.1	Change in the manufacturer of a starting material/reagent/ intermediate used in the manufacturing process of active substance or change in the manufacturer (including where relevant quality control testing sites) of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier.	**Comment and rationale**: Although an option of a change in manufacturer of starting material/reagent/intermediate is made in the guideline, a separate sub-category has not been assigned to such changes. It is, therefore, difficult to classify such changes (type IA, IB or II), particularly when these changes do not pertain to manufacturer from same pharmaceutical group (as in B.I.a.1.a), are not from different routes of synthesis (as in B.I.a.1.c), do not require viral assessment (as in B.I.a.1.d) and are not used in the manufacture of a biological/immunological product (as in B.I.a.1.e). A separate variation case should be included for the introduction of manufacturer of such type of starting material/reagent/intermediate. Further this category should also accommodate change in manufacturer of solvent used in the manufacture of active substance. **Proposed change (if any)**: *New variation case* Introduction of a manufacturer (from different pharmaceutical group) of starting material/reagent/solvent/intermediate used in the manufacture of active substance, when the route of synthesis is not substantially different, the viral safety and/or TSE risk assessment is not required and it is not used in the manufacture of biological/immunological product.
B.I.a.1.k	New storage sites of Master Cell Bank and/or Working Cell Banks	**Comment and rationale**: It should be specifically mentioned that the new storage sites may refer to addition or replacement. A separate variation for deletion of existing storage site should also be provided. **Proposed change (if any)**: New storage sites of Master Cell Bank and/or Working Cell Banks (addition or replacement). and *New variation case:* Deletion of storage sites for Master Cell Bank and/or Working Cell Banks.

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B.I.a.3.a	Up to 10-fold increase compared to the currently approved batch size	**Comment and rationale**: The current variation guideline does not take into account the proposal of multiple batch sizes with in the 10 fold increase. The acceptability/non-acceptability of multiple batch sizes in a single variation should be clarified as one of the conditions of this type IA variation.
B.I.a.4	Changes to the in-process tests or limits applied during the manufacture of the active substance	**Comment and rationale**: A variation case regarding addition of new in-process test and limits which involve a biological/immunological/immunochemical method, should be included. **Proposed change (if any)**: *New variation case:* Addition of a new in-process test and limits which involve a biological/ immunological/immunochemical method or a method using a biological reagent for a biological active substance.
B.I.b.1	Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance	**Comment and rationale**: This variation case should also take into consideration the change in the specifications of solvents used in the manufacturing process. **Proposed change (if any)**: Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent/solvent used in the manufacturing process of the active substance.
B.I.b.2	Change in the test procedure for active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance	**Comment and rationale**: This variation case should also take into consideration the change in the test procedure of solvents used in the manufacturing process. **Proposed change (if any)**: Change in the test procedure for active substance, starting material/intermediate/reagent/solvent used in the manufacturing process of the active substance
B.I.c.2.d	Addition or replacement of a specification parameter as a result of a safety or quality issue	**Comment and rationale**: In order to make this category more specific, this variation should also include reference to inclusion of corresponding test procedure. **Proposed change (if any)**: Addition or replacement of a specification parameter with its corresponding test procedure as a result of a safety or quality issue

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B.I.c.2	Change in the specification parameters and/or limits of the immediate packaging of the active substance	**Comment and rationale**: This variation should also include widening of the approved specification limits of the immediate packaging of active substance. **Proposed change (if any)**: *New variation case:* Change outside the approved specification limits for the immediate packaging of the active substance
B.I.d.1, 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 the testing	**Comment and rationale**: It is not clear from the text of the condition 2 if reduction in the frequency of testing also includes the reduction in the total duration of the stability studies. **Proposed change (if any)**: 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 the testing. However, reduction in total duration of stability study is acceptable based on suitable justification.
B.II.a.2.a, condition 2	Release and end of shelf-life specifications of the product have not been changed (except for dimensions)	**Comment and rationale**: Since the referred variation is with respect to change in shape or dimensions, the condition 2 should also include exception of appearance due to change in shape **Proposed change (if any)**: Release and end of shelf-life specifications of the product have not been changed (except for dimensions or appearance)
B.II.b.2.c.2	Replacement or addition of a manufacturer responsible for importation and/or batch release including batch control/testing	**Comment and rationale**: There is no reason to re-categorize this change as Type II. This categorisation seems to be a transcription error since the conditions are laid down for this change. If this change is not intended to be categorised as Type II, the required documentation should be listed.
B.II.b.3.f	Minor change in the manufacturing process of an aqueous oral suspension	**Comment and rationale**: This variation can also include minor change in the manufacturing process of semi-solid products and emulsions. **Proposed change (if any)**: Minor change in the manufacturing process of an aqueous oral suspension, semi-solid products and emulsions.

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B.II.b.3	Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of finished product	**Comment and rationale**: In many instances, the manufacturer may decide to delete the overages from the product based on the experience on multiple batches after approval. Therefore, the deletion of overages used for the active substance should also be incorporated as a change in the manufacturing process. **Proposed change (if any)**: *New variation case:* Deletion of overage that is used for active substance.
B.II.b.3	Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of finished product	**Comment and rationale**: In many instances, there are minor changes in the manufacturing process of biological/immunological medicinal products which do not require an assessment of comparability e.g. addition of redundant filter in the sterile filtration. This should be incorporated as separate variation in the change in manufacturing process. **Proposed change (if any)**: *New variation case:* The product is a biological/immunological medicinal product and the change does not require an assessment of comparability.
B.II.b.3	Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of finished product	**Comment and rationale**: A separate variation cases regarding minor change in the manufacturing process of sterile finished product and modified release dosage form should be included. **Proposed change (if any)**: *New variation cases:* Minor change in the manufacturing process of sterile finished product. and Minor change in the manufacturing process of modified release dosage form.

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B.II.b.3	Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of finished product	**Comment and rationale**: A separate variation cases regarding minor change in the manufacturing process of sterile finished product after primary packaging should be included. **Proposed change (if any)**: *New variation case:* Minor change in the manufacturing process of sterile finished product after primary packaging.
B.II.b.3	Change in the manufacturing process of the finished product, including an intermediate used in the manufacture of finished product	**Comment and rationale**: There may be change in holding time of an intermediate during the manufacture of finished product. The variation guideline should take into account such changes. **Proposed change (if any)**: *New variation case:* Change in holding time of an intermediate during manufacture of finished product.
B.II.b.4.a	Up to 10-fold increase compared to the currently approved batch size	**Comment and rationale**: The current variation guideline does not take into account the proposal of multiple batch sizes with in the 10 fold increase. The acceptability/non-acceptability of multiple batch sizes in a single variation should be clarified as one of the conditions of this type IA variation.
B.II.b.5	Change to in-process tests or limits applied during manufacture of the finished product	**Comment and rationale**: Several times, the drug product manufacturer may introduce limits to the existing in-process controls (earlier mentioned as report results) due to reasons like deletion of certain tests from intermediates. A separate variation case regarding this should be included in the change to in-process controls or it should be clarified if such changes can be classified under B.II.b.5.a. as tightening of in-process limits. **Proposed change (if any)**: *New variation case:* Introduction of limits to already approved in-process controls with no pre-defined limits.

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B.II.b.5	Change to in-process tests or limits applied during manufacture of the finished product	**Comment and rationale**: In many instances, there is addition of new tests and limits that involves a biological/immunological/immunochemical method. This should be incorporated as separate variation in the change to in-process controls. **Proposed change (if any)**: *New variation case:* Addition of new tests and limits that involve a biological/immunological/immunochemical method.
B.II.c.1	Change in the specification parameters and/or limits of an excipient	**Comment and rationale**: A separate variation case regarding addition or replacement of a specification parameter which involves a biological/ immunological/immunochemical method should be included. **Proposed change (if any)**: *New variation case:* Addition or replacement of a specification parameter of a specification with its corresponding test method in a biological/immunological product, where the test method is a biological/immunological/immunochemical method or a method using a biological reagent (does not include standard pharmacopoeial microbiological methods).
B.II.c.3.a	Change in source of an excipient or reagents from TSE risk material to vegetable or synthetic origin	**Comment and rationale**: The amended relevant sections of the dossier should also be listed as one of the required documentation. **Proposed change (if any)**: *New documentation 3:* 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)

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B.II.d.1	Change in the specification parameters and/or limits of the finished product	**Comment and rationale**: A separate variation case regarding addition or replacement of a specification parameter which involves a biological/immunological/immunochemical method should be included. **Proposed change (if any)**: *New variation case:* Addition or replacement of a specification parameter with its corresponding test method in a biological/immunological product, where the test method is a biological/ immunological/ immunochemical method or a method using a biological reagent for a biological active substance.
B.II.d.1	Change in the specification parameters and/or limits of the finished product	**Comment and rationale**: A separate variation case regarding change in microbial limits and methods in order to comply with current Ph. Eur. 5.1.4 and Ph. Eur. 2.6.12 and 2.6.13 should be included. EMA scientific guideline "Quality of medicines questions and answers: Part 1" suggests to submit 2 variations to change limits and methods, which in fact should be treated as a single change and therefore be allowed under 1 class. **Proposed change (if any)**: *New variation case:* Change in microbial limits and methods in order to comply with the current harmonised Ph. Eur. 5.1.4 and Ph. Eur. 2.6.12 and 2.6.13.
B.II.e.2	Change in the specification parameters and/or limits of the immediate packaging of the finished product	**Comment and rationale**: This variation should also include widening of the approved specification limits of the immediate packaging of finished product. **Proposed change (if any)**: *New variation case:* Change outside the approved specification limits for the immediate packaging of the finished product

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B.II.f.1	Change in the shelf-life or storage conditions of the finished product	**Comment and rationale**: There could be change in the storage period of finished product packed in the bulk pack. Such type of changes should also be incorporated either as part of B.II.f (stability) or B.II.b (manufacture). **Proposed change (if any)**: *New variation case:* Change in the storage period of finished product packed in bulk pack where specified in the dossier.
B.II.f.1.e, 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 the testing	**Comment and rationale**: It is not clear from the text of the condition if reduction in the frequency of testing also includes the reduction in the total duration of the stability studies.
B.IV	Medical devices	**Comment and rationale**: Generally, the information related to CE marked device for human medicinal products such as specifications, material of construction, accessories (e.g. needles) are submitted as regional information in section 3.2.R of the MAA. The variation guideline does not address the changes in such parameters for a CE marked device for human medicinal products. For e.g. it is likely that an applicant may change the specifications of a device after informing the notified body. In such instances, the variation guideline does not include scope of notification to the agency in support of MAA. It is, therefore, suggested to include a separate variation cases to encompass these changes. **Proposed change (if any)**: *New variation cases:* • Change in specification parameters and/or limits of the CE marked devices for human medicinal products. • Change in material of construction of a CE marked device for human medicinal products. • Change in accessories such as compatible needles that can be used with the CE marked device for human medicinal products.