Sundhedsstyrelsen
Danish Health and Medicines Authority

European Commission,
DG Health and Consumers,
Unit D5 'Medicinal products – authorisations, EMA

Danish comments - Public Consultation Paper – Review of the Variations Guidelines

July, 11 2012

Our ref: Jakob Lundsteen

The Danish Health and Medicines Authority welcomes the Commission initiative on revising the Variations Guidelines and we thank you for this opportunity to comment on the proposals.

We have the following comments:

The classification guideline, sent for public consultation, is noted not to be the complete guideline as the preliminary text in the current guideline is not presented in the document sent for consultation. If it is the intention of the Commission to delete the introduction, a lot of valuable information will be lost and would need to be included elsewhere in regulatory guidelines. Had this text been included we would have presented a series of comments.

Regarding change *B.I.a.4.c* (page 16-18) *condition number 7*, the wording should be updated to include in-process tests like temperatures, pH, loss on drying, impurities, assay, intermediates etc. rather than specification parameters of a final active substance. Furthermore, under *documentation number 5,* it is not clear what the purpose is with the declaration or justification requirement. Is a parameter only non-significant, if previously approved risk assessment has been performed (via another variation/application)? We foresee only to receive justifications that the parameters are obsolete, which is the current procedure by the applicants.

With regard to *documentation number 6* under change *B.I.b.1.d* (page 18-19) and all variations including the same documentation (B.I and B.II), it is not clear what the purpose is with the declaration or justification requirement. Is a parameter only non-significant, if previously approved risk assessment has been performed (via another variation/application)? We foresee only to receive justifications that the parameters are obsolete, which is the current procedure by the applicants.

In view of the recent discussion on the ASMF procedures, we suggest to include a type II variation for updates of the ASMFs in line with current guidance already published by HMA (Question and Answer number 3.4 in

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"Q/A list for the submission of variations according to commission regulation (EC) 1234/2008").

Regarding change *B.II.b.1.c* (page 35) and *B.II.b.4.d* (page 41), we suggest using the defined term "non-standard" manufacturing process instead of "complex" manufacturing process.

Change *B.II.b.2.c.2.* (page 38) concerns a type II variation and no conditions should be listed.

With regard to change *B.II.b.4.a* (page 42) *condition number 7,* the wording "unless otherwise justified" is not clear and should be deleted from the text line 5 and 7 from the top. There is no guidance for when a lower batch size would be acceptable and should not be discussed in a type IA variation.

Regarding change *B.II.d.1.h* and *B.II.d.1.i* (page 50), the definition of B.II.d.1.i is included in the definition of B.II.d.1.h. A type IB variation is preferred, as specification limits is not always provided in general monographs.

We find that it is unclear which change *B.II.d.2.f.* (page 52) concerns.

Regarding the category *B.II.f.1* (page 60) a type II variation should be identified concerning reduction of the shelf life of the finished product following quality, safety or efficacy issues including stability concerns during on-going stability studies. Furthermore a type II variation should be identified concerning change to the storage precaution of the finished product or the diluted/reconstituted product following quality, safety or efficacy issues including stability concerns during on-going stability studies. The reasons for this, is that change in storage conditions (restriction from e.g. none to 2-8 degrees) and reduction of shelf life (from 5 to 3 years) as a result of a quality, safety or efficacy issue (Out of Specification results seen for e.g. impurities or dissolution and withdrawal of the medicinal product from the market necessary due to efficacy or safety concerns) should be a type II variation according to the variation regulation definition art. 2,3 *"Major variation of type II means a variation which is not an extension and which may have a significant impact on the quality, safety or efficacy of the medicinal product concerned"*. And annex III c) *variations related to changes outside the range of approved specifications, limits or acceptance criteria; d) variations related to substantial changes to the manufacturing process, formulation, specifications or impurity profile of the active substance of finished medicinal product which may have a significant impact on the quality, safety or efficacy of the medicinal product.* A fast procedure is possible with a 30 day type II procedure

On changes *B.III.1.a.5* and *B.III.1.b.4* (page 66), we would like to comment that change in supplier also can be applied for as a type A7, which is considered more appropriate. It is not clear what the difference is between A7 and B.III.1.a.5/B.III.1.b.4., and in addition, suppliers of excipients are not registered.

Regarding change *B.III.1.a.2* and *B.III.1.a.4* (page 66), we find that is unclear why condition 11 does not apply.

Regarding change *B.III.1.b.1* (page 66), we are find that it is not clear why condition 11 is included,

Thank you for taking our comments into consideration.

Best regards,

Jakob Lundsteen