European Medicines Agency
<Unit>

14th July 2012

SUBMISSION OF COMMENTS ON

Review of the Variations Guidelines

COMMENTS FROM:

Consolidated comments from Alcon Laboratories UK Ltd **Siama Aslam**

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

Comments should be sent to the EMEA electronically and in word-format (not pdf).

1. GENERAL COMMENTS

Stakeholder No. *<to be completed by EMEA>*	**General Comment (if any)**	**Outcome (if applicable)** *<to be completed by EMEA>*
	Any provisions of the draft update prepared and shared in track changes mode would be very much appreciated.	

2. SPECIFIC COMMENTS ON TEXT

Change reference	**Stakeholder No.** *<to be completed by EMEA>*	**Comment and Rationale; proposed changes** *<if changes to the wording are suggested, they should be highlighted using "track changes">*	**Outcome** *<to be completed by EMEA>*
A.3		Change in the name of the active substance or of an excipient **Comments:** Documentation 1: what is meant by '*proof that the change is in line with the Ph.Eur.*' Will a copy of the respective Ph. Eur. Monograph be sufficient?	
A.5		Change in the name and/or address of a manufacturer of the finished product including importer, batch release or quality control testing sites. **Comments**: Under which subcategory (a or b) should a name change of a sterilization site be placed?	
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….. **Comments**: 1.Documentation 8: For a manufacturing site outside the EU/EEA without an MRA … Would a GMP certificate or inspection report issued by an authority with which an MRA is in place (like the TGA, Swissmedic) or an inspection report from the FDA also be acceptable? This also seems contradictory to directive 2011/62/EU (article	

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		46b(2), in which it is stated that active substances shall only be imported if they are accompanied by a written declaration from the exporting third country which confirms that the manufacturing plant meets standards of good manufacturing practices and controls equivalent to those in the EU. 2. Sub-category h) – Is documentation from "Documentation 2" relevant for sub-category h? As it is only a site change (no change in sterilization process) and batch data are included in documentation 4.	
B.I.a.4 g)		**Change to in-process tests or limits applied during the manufacture of the active substance.** **g) Change to the limits....** **Comments:** The word processes should be changed to process.	
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. **Comments:** Documentation 7: What is meant by "*any new impurity control should be in line with the Ph.Eur or National Pharmacopoeia of a Member State*"? Is a reference made to Ph.Eur. 5.10?	
B.I.c		**Container closure system**	

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		Comments: Changes in the quantitative or qualitative composition of the primary packaging material, changes in the specifications or test procedures for the primary packaging material can under certain conditions be classified as a type IA variation. No variation category is included on a change in secondary packaging material (and historically details on the secondary packaging are sometimes included in the product dossiers), this change them by default is a type IB variation, which does not seem logical. Can a variation category be added for changes to the secondary packaging of a drug substance (when mentioned in the dossier)?	
B.I.f.1		Introduction of a post approval change management protocol related to the active substance **Comments**: Documentation 3, what is expected here. Degree of detail, template, other, …	
B.I.f.4		Implementation of changes foreseen in an approved change management protocol related to the active substance **Comments**: What is meant by this note? Please further clarify by an example.	

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B.II.b.1		Finished Product Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product. **Comments**: Sub-category f - site where any manufacturing… Documentation 6 appears to only be applicable for suspensions/ointments but it seems not required for only manufacturing site changes where there are no (critical) changes to the manufacturing process. Moreover, in category B.II.b.3 ophthalmic suspensions / ointments do not seem to fall within the scope (aqueous oral suspensions) of the same required documentation. Imaging techniques other than micro-scoping imaging might be in place for determination of distribution profiles of particles. Can we therefore add, if appropriate other imaging techniques?	
B.II.b.2.c) 2		Change to importer, batch release arrangements and quality control testing of the finished product Sub-category C.2. Including batch control / testing **Comments**: Currently batch release in this case is specified as a Type IAIN and in the draft documents is listed as a Type II. Why is this?	
B.II.c.5		Change in manufacturer of a novel excipient **Comments**: Subcategories a) and b): How long does a novel excipient remain novel? For well-	

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		known excipients the manufacturer can be changed without variation. .	
B.II.d.1		Change in the specification parameters and/or limits of the finished product. **Comments**: Subcategory h) – subcategory e): What is meant by "*updated general monograph of the Ph.Eur.*"? Is this exclusive monographs on dosage forms?	
B.II.d.2		Change in the procedure for the finished product **Comments**: Sub-category e – what is meant by "updated general monograph in the Ph.Eur"?	
B.II.e.1		Change in immediate packaging of the finished product **Comments**: Subcategory b): what is meant by '*type*' of container and '*new container*'? Also, shouldn't '*deletion of an immediate packaging container*' be a separate category?	
B.II.h.1		Introduction of a post approval change management protocol related to the finished product **Comments**: Document 3 – what is expected here? Degree of detail, templates?	
B.II.h.4		Implementation of changes forseen in an approved change management protocol related to the finished product.	

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		Comments: What is meant by this note? Please further clarify by an example.	
B.III.1		Submission of a new or updated Ph.Eur. certificate of suitability or deletion of Ph. Eur. certificate of suitability... **Comments:** Subcategory a) 5. Deletion of certificates : is this the category to use for deletion of an active substance manufacturer with a CEP or is this part of category A.7 deletion of manufacturing sites? Subcategory a) 6. : We consider this applicable only for injectable products. Can we exclude ophthalmics/otics? Condition 11: We consider this applicable only for injectabilia because of the requirement of "free from bacterial endotoxins". Can we exclude ophthalmics/otics?	