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European Commission
Health and Consumers Directorate-General
Unit D5 'Medicinal products – authorisations, EMA'
E-mail: SANCO-VARIATIONS-GUIDELINES@ec.europa.eu

13 July 2012

7 Giralda Farms, Suite 1001
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Re: June 2012: Public Consultation Paper on the review of the Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

Dear Sir or Madam:

The following comments are submitted on behalf of Bausch + Lomb. On 14 June 2012, the Commission posted a public consultation on European Commission Consultation on Variations Regulation Update (includes update for PV Legislation). With this public consultation, the Directorate General for Health and Consumers intends consulted stakeholders to review the guidelines on the details of the various categories of variations.

Bausch + Lomb is one of the best-known and most respected healthcare companies in the world. Our core businesses include contact lenses and lens care products, ophthalmic surgical devices and instruments, and ophthalmic pharmaceuticals. Founded in 1853, our company is headquartered in Rochester, N.Y., and employs more than 10,000 people worldwide. Our products are available in more than 100 countries including throughout the European Union.

We appreciate the opportunity to provide comments on the proposed revised guideline and support the Commission in its efforts to create updated guidelines that reflect advancement in practices relating to the variation categories for medicinal products for human use. In that respect, we offer the following comments:

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Comment #1- Quality Changes/Active Substances, Section B.I.a.1.g (p. 10)

To ensure consistency in its interpretation, we recommend that B.I.a.1.g be clarified to specify that the Type II assignment is for API changes that may "adversely impact the quality, safety, or efficacy of the medicinal product." We recommend the following revision:

> 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 substances section of the dossier~~ may adversely impact the quality, safety, or efficacy of the medicinal product requiring a significant update to the relevant active substances section of the dossier.

Comment #2 – Manufacture, Section B.II.b.2.c.2. (p. 38): Change to importer, batch release arrangements and quality control testing of the finished product

In the draft guideline "2. Including batch control/testing" is designated as a Procedure Type II change. However, in the current guideline, "Including batch control/testing" (see image below of p. 34, Section B.II.b.2.b.2) is designated as Procedure Type IA_{IN}. Please confirm if the revision in the draft from a Type IA_{IN} to Type II was intentional or if it was inadvertently changed during the revision process. We believe this is a transposition error, particularly since Type II filings would not have Conditions to be fulfilled criteria as presented in the draft. A correction back to Type IA_{IN} would also then include the Documents to be supplied as "1, 2, 3, 4, 5".

For reference, the current guideline is as follows:

B.II.b.2 Change to batch release arrangements and quality control testing of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Replacement or addition of a site where batch control/testing takes place	2, 3, 4	1, 2, 5	IA
b) Replacement or addition of a manufacturer responsible for batch release			
1. Not including batch control/testing	1, 2	1, 2, 3, 4, 5	IA_{IN}
2. Including batch control/testing	1, 2, 3, 4	1, 2, 3, 4, 5	IA_{IN}
3. Including batch control/testing for a biological/immunological product and one of the test methods performed at that site is a biological / immunological / immunochemical method.	Excerpt from Current Guideline		II

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For reference, the proposed June 2012 guideline revision is as follows:

B.II.b.2 Change to importer, batch release arrangements and quality control testing of the finished product	Conditions to be fulfilled	Documentation to be supplied	Procedure type
a) Replacement or addition of a site where batch control/testing takes place	2, 3, 4, 5	1, 2, 5	IA
b) Replacement or addition of a site where batch control/testing takes place for a biological/immunological product and one of the test methods performed at that site is a biological / immunological / immunochemical method			II
c) Replacement or addition of a manufacturer responsible for importation and/or batch release			
1. Not including batch control/testing	1, 2, 5	1, 2, 3, 4, 5	IA
2. Including batch control/testing	1, 2, 3, 4, 5		II

Comment #3 - Manufacture, Section B.II.b.3 (p. 39): Change in the manufacturing process of the finished process, <u>including an intermediate used in the manufacture of the finished product</u>

To enhance the utility and consistency with other available guidance, we recommend the inclusion of "unforeseen variations" as included in the "CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008" (see also CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) 1234/2008 (June 2012)

Specifically, we recommend inclusion of the following into the final guideline:

CMDh Recommendation for classification of unforeseen variations according to Article 5 of Commission Regulation (EC) No 1234/2008				
Section of the Classification Guideline	Date issued	Summary of the proposed change	Proposed classification	Proposed conditions, where relevant
B.II.b) Manufacture				
B.II.b.3.b	26.04.2010	Change in the manufacturing process of the finished product: to move the sterilizing filtration from A/B to C.	II	N/A
B.II.b.3.z	22.03.2010	Change in the manufacturing process of the finished product: minor change in the manufacturing process of modified release oral dosage form.	IB	N/A
B.II.b.3.z	26.04.2010	Change in the manufacturing process of the finished product: minor change in the manufacturing process of solution for injection/infusion.	IB	N/A
B.II.b.3.z	26.04.2010	Minor change in the manufacturing process of the finished product- Change in the holding time of an intermediate.	IB	N/A

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Comment #4 - CEP/TSE/Monographs, Section B.III.1 (p. 66): Submission of a new or updated Ph. Eur. Certificate of suitability or deletion of Ph. Eur. certificate of suitability / Conditions to be fulfilled item #11

As written, the condition to be fulfilled item 11 is general and broad and may inadvertently result in new and unnecessary conditions to be fulfilled for sterile products. We recommend that the guidance clarify conditions to be fulfilled item 11 as "injectables" for the applicable pharmaceutical form (i.e., parenteral medicinal product, instead of sterile medicinal product). As such, we recommend the following revision:

> **Conditions to be fulfilled:**
>
> 11. If the active substance is a not a sterile substance but is to be used in a ~~sterile~~ parenteral medicinal product then according to the CEP it must not use water during the last steps of the synthesis or if it does the active substance must also be claimed to be free from bacterial endotoxins.

Comment #5 – Safety, Efficacy, Pharmacovigilance Changes, Section C (pp. 76-82)

In this Pharmacovigilance section, it is unclear which variation type would apply when the new text on the reporting mechanism is implemented (i.e., the statement to encourage reporting of suspected adverse reactions for patients and Healthcare Professionals applicable to all medicinal products in the SmPC and PL). Please clarify the variation type to be applied.

We trust these comments will enhance the clarity of the guideline when final.

Sincerely,

Kimberly Belsky
Executive Director, Policy and Communication
Global Regulatory Affairs – Pharmaceuticals