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SUBMISSION OF COMMENTS ON Commission Regulation (EC) No.../.. of [...] concerning the examination of amendments to the terms of marketing authrorisations for medicinal products; Version 24 October 2007, Deadline for Public Consultation: 04 January 2008

COMMENTS FROM: Bristol-Myers Squibb

GENERAL COMMENTS

For submission of group of Type IAs within the proposed 12-month reporting time, no submission date is specified. We propose that the MAH set the date and additional text be included that specifies this matter.

The draft detailed Guideline referred to in Article 6(1)(a) (p. 27 - 48) has taken into account reduction of regulatory burden based upon risk assessment for changes to drug product (#s 19, 20, 21, 22, 24, 31, 33), which is a welcome change. However, the same philosophy has not been applied to changes for drug substance (#s 10, 11, 12, 13 & 14). The draft Guideline does not differentiate the variation categories for starting materials, intermediate, or reagents from API, which does not reflect a risk-based approach to evaluation of changes. In addition, there could be some examples of changes for biologics that would result in Type IB variations, which would be appropriate for process changes for which bioanalytical comparability, only, would be necessary to be demonstrated.

SPECIFIC COMMENTS ON TEXT

GUIDELINE SECTION TITLE

Line no[1]. + paragraph no.	**Comment and Rationale**	**Proposed change (if applicable)**
p. 5	Article 4, #2 Please clarify requirements for a Type II. If the default category is now a Type IB, then it is not clearly specified that the reporting category for changes that do not meet the conditions for a Type IB are to be notified as a Type II.	Add text clarifying that if the conditions for a Type IB are not met, then the variation reporting category is a Type II.

[1] Where available

p. 10	Second paragraph: "..., the variation must be evaluated according to the type II procedure (Figure 4)." (Also covered by Articles 9.5, 13.5 and 18.5 of proposed Regulation) Please clarify that no additional documentation will be requested as a result of the change of classification.	Add text clarifying whether or not additional documentation will be requested as a result of the change in classification.
p. 18	Article 22: Implementation by economic operators Article 22, Item 1 specifies that Type IA variations may be implemented anytime before the completion of the procedure, however, no mention of the implementation time for a Type IA_{IN} is included in this Article. .	Please clarify that both type IA and Type IA_{IN} can be implemented anytime before the change is made.
p. 18	Article 22: Implementation by economic operators A minor variation of type IA may be implemented anytime before completion of the procedures laid down in Articles 8, 12 and 17.	Please clarify that the variations may also be implemented after the completion of the procedures laid down in Articles 8, 12 & 17
p. 23	Annex I The text for Annex I(c) is unclear. The phrase "slightly different molecular structure" is subject to gross interpretation. For example, a minor modification to a manufacturing process may result in a *slightly* different glycosylation profile. Based upon the current text, this change may now be interpreted as requiring an extension (particularly at the national level)	Add clarifying text or examples to support a more consistent interpretation of 'slightly'.
p. 24	Annex II 4. All variations in the group relate solely to changes to the SmPC, labelling and package leaflet or insert. Changes to the RMP that are related to the changes in SmPC, labelling and/or package leaflet should be part of the variations	Add text to Item 4 to indicate that all variations in the group relate solely to changes to the SmPC, labelling and package leaflet and the related update of the Risk Management Plan
p. 24	Annex II 5. All variations in the group are changes to an Active Substance Master File, Vaccine Antigen Master File or Plasma Master File. If grouping of changes to ASMFs is acceptable, then changes to an open Module 3.2.S should be eligible to be grouped as well.	Add text to Item 5 to indicate that all variations in the group are changes to an Active Substance master File, Module 3.2.S, Vaccine Master File or Plasma Master File.

p. 27 - 48	Draft Detailed Guideline on Variations Referred to in Article 6(1)(a) - Draft Detailed Guideline on Variations Referred to in Article 6(1)(a) 1. Documentation requirements are removed, which could lead to interpretation of requirements to the national level (in the case of national registrations and decentralized products). 2. Whilst the concept of issuing these as guidelines is good with respect to future flexibility for amendments there is a fear that not having legal force could lead some Member States to add local requirements for nationally approved and MRP products thereby negating the aim of a single harmonised system.	Include dossier requirements to the same level of detail as the current Guideline on Dossier Content of Type IA and IB Notifications
p. 30 - 31	#10, 11, 12, 13 & 14 There is no differentiation of the variation categories for starting materials, intermediate, or reagents from API, which is not in accordance with the risk associated with such changes. For example, replacement of a test procedure for a reagent would present considerably less risk to product quality than the same change for an API. Changes to the API or penultimate API would present the most risk to product quality and should be categorized accordingly.	Differentiate requirements for modifications to starting materials, reagents, intermediates from API to reflect risk associated with changes. Propose that changes to starting materials, reagents and intermediates are notified as Type IA variations.
p. 29-30	#10 If the assumption that if the conditions for a Type IB are not met, then the change is to be reported as a Type II, then all minor changes to the manufacturing process for a biological are still categorized as a Type II variation. This categorization does not account for a risk assessment of potential impact to product quality.	Provide clearer categorization for specific changes to biological products that present minimal risk to product quality. There could be some examples of process changes for biologics that would result in Type IB variations. In situations where comparison of relevant quality attributes, pre- and post-change product are highly similar and considered comparable, the change is unlikely to have an adverse impact on product quality.
p. 34	#18 Conditions do not account non-solid oral dosage forms, such as topicals. For example, dissolution testing will not account for absorption of dermatological products.	Add a condition excluding non-solid oral dosage forms from a Type IA.
p. 47	New.6 (from the *Draft Detailed Guideline Referred to in Article 6(1)(a): Conditions for Classification of Variations*) No mention of requirements for changes within an approved design space is included. Please specify that for changes within an approved design space no notification is required. If such detail is not provided, then it is possible there may be national interpretations requiring notification for changes within a design space.	Add a set of conditions to be fulfilled to indicate that changes within an approved design space (or proven acceptance range) do not require notification, as per ICH Q8 working within a design space is not considered a change (ICH Q8, p.1)..

p. 47	New.7 Administrative change in the SmPC, labelling and package leaflet/insert It is not clear why an administrative change to the labelling or package leaflet should change from the current procedure (notification according to Article 61(3) to a type IA $_{IN}$ variation)	Revise the description for New 7 to read as follows: New 7 Administrative changes in the SmPC, ~~labelling and package leaflet/insert~~
p. 48	New 8. Change in the SmPC, labelling and package leaflet/insert following an urgent safety restriction, class labelling, or a periodic safety update report Please add the inclusion of the corresponding update of the Risk Management Plan (RMP)	Revise the description for New 8 to read as follows: New 8. Change in the SmPC, labelling and package leaflet/insert and corresponding change in Risk Management Plan following an urgent safety restriction, class labelling or periodic safety update report