EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

<Date of submission> 13 July 2012

Submission of comments on '<PUBLIC CONSULTATION PAPER, REVIEW OF THE VARIATIONS GUIDELINES>' (**REGULATION (EC) No 1234/2008 ARTICLE 4: REVIEW OF THE VARIATIONS GUIDELINES**)

Comments from:

APIC

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

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

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1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	Throughout the document "Union" is used as either a synonym for "European Union" or for "EU/EEA". It should be made clear in each case what the correct term is.	

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Outcome *(To be completed by the Agency)*
A.4		Comment: Unclear what is meant with the added "or a manufacturer of a novel excipient". Do changes in name and/or address of manufacturers of non-novel excipients not need to be notified? Please clarify. Proposed change (if any):	
A5		Comment: It is not clear which manufacturing activities are mentioned here. If the manufacturer of the finished product is affected by the change in name and/or address, but this site is not responsible for the batch release site, will this change than fall under b) All other? If the condition for this change is that at least one of the activities should be the batch release, the description of the change should be reworded.	
B.I.a.1 b)		Comment: Why does the Commission delete the word "new"? A clarification of this case is needed. Does it mean that this manufacturer was previously incorporated in the MA dossier and that change consists in having now a ASMF for this manufacturer? At APIC, we think that if the manufacturer follows the same synthetic route that previously described and	

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		that the change has no impact of the API quality this variation should be classified as Type IB. The introduction of a new manufacturer supported by an ASMF is then no more scheduled by the Guideline. It is then now a Type IB by default. Proposed change if any: Classify this variation as Type IB	
B.I.a.1 g)		Comment: There is a mix in this point between change of manufacturer and other changes like change in the manufacturing process or analytical or stability or…. Full documentation should be submitted only if specification and impurity profile is different Proposed change (if any) B.I.a.1.g: Introduction of a new manufacturer of the active substance that is not supported by an ASMF	
B.I.a.1h		Comment: We do not think that a change in the sterilisation site will affect the synthetic route or the active substance specifications Proposed change (if any) Documentation change B.I.a.1 h): 1 4 5 8	
B.I.a.4 Change to in-process tests or limits applied during the manufacture of the active substance		Comment: Non-critical process parameters in the API manufacturing of NCEs are usually not reported anyway. Therefore changes of these parameters are no subject of variations at all. Proposed change (if any): Delete line g) and corresponding conditions for NCEs.	

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line g)			
B.I.b c		Comment: The addition of a specification has not impact on the quality of the API. Why do you add documentation 5? Proposed change (if any) Documentation B.I b) c: 1 2 3 4 7	
B.I.c Documentation 3		Comment: "Legislation of the Union" Proposed change (if any): EU legislation	
B.I.e.1.a)		Comment: It is unclear why a design space variation is restricted to one unit operation. The corresponding change for drug product allows for "One or more" Proposed change (if any): "One or more"	
B.I.e.1 Documentation 1		Comment: Unclear what is meant by "product". If results from the drug product manufactured with active substance using the proposed design space is meant this would stop innovation in the dedicated API manufacturing industry. Proposed change (if any): "… Results from drug substance, process…"	
B.I.f.4.b)		Comment: Omitted the word "data"	

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		Proposed change (if any): …"no further supportive data and"…..	
B.III.1 Condition 3		Comment: Not all new or updated certificates from manufacturers using materials of human or animal origin should require assessment of the risk with respect to potential contamination with adventitious agents: 1. The risk can in certain instances be adequately controlled at the level of the active substance and then does not need to be reassessed for the drug product. 2. . The updated certificate may relate to administrative change or editorial changes to the appended analytical procedure(s) and therefore not change the risk with respect to potential contamination with adventitious agents. In both cases the implementation of the certificate should only require immediate notification, as would be the requirement for the same change when the active substance documentation is included in the MA dossier. Proposed change (if any): 3. Where materials of human or animal origin are used in the process, the manufacturer does not use any new supplier or changed manufacturing process for which a new assessment is required of viral safety data or of compliance with the current Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products.	

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B.III.1 a) 6 and B.III.1 b) 5		Comment: EU Commission needs to clarify these 2 categories. Who is the assessor? EDQM or National Authorities/EMA? We would like to avoid a duplicate review of the same data (which is in line with the principle of simplification and flexibility of the variations regulations). If EDQM does not review these data, it should be included in the MA dossier, in the drug product section and change considered as change impacting the viral safety assessment of the drug product. A change already evaluated by EDQM should remain type IA.	
C.I.8.a) Condition 1, 2		Comment: "Union" may not be clear Proposed change (if any): Replace "Union" with "EU/EEA" as is used elsewhere in the document.	

Please add more rows if needed.