EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

20 April 2012

Submission of comments on 'Delegated act on the principles and guideline of good manufacturing practice for active substances in medicinal products for human use' (Sanco.ddg1.d.6(2012)73176)

Comments from:

Name of organisation or individual
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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)*
	EFPIA agrees with the objective to bring coherence into the regulatory framework governing GMPs for medicinal products, investigational medicinal products and active pharmaceutical ingredients (API). However EFPIA is concerned that the various differences in applicability of 'medicinal product GMPs' vs. 'API GMPs' as listed below, will complicate the overall GMP interpretation and hence contradict the purpose of having a clear legal framework. In order to avoid ambiguity and reflect the differences a separate section in Directive 2003/94/EC specific to APIs or a complete independent directive should be introduced. This could easiest be achieved by simply referring to the technical details of Part II of the EudraLex Volume 4 (EU-GMP's), which are implementing the international harmonised and agreed ICH Q7 guidance. EFPIA would also like to reference the EFPIA position paper 'GMP for APIs' provided at the GMDP IWG - Interested Parties Meeting, November 23, 2011, Item 3.4c.	
	EFPIA recommends adopting a clear definition for 'starting material' which is - 'API-starting material' (i.e. raw material; see ICH Q7) and 'Starting material' (i.e. APIs, excipients, see part 1 of the EU GMPs).	

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 (if applicable) ***(To be completed by the Agency)***
Consultation item n° 1: Do you agree with this appraisal and approach? Please comment.		EFPIA has strong reservations with the proposal to extend all provisions of the Directive 2003/94/EC to active substances as is. However, the structure of the content of the provisions must ensure the differences are clearly reflected. The directive provides the legal basis for the interpretation of the EU-GMP. Such differences may include for instance: • Various significant differences in interpretation of 'drug product GMPs' vs. 'drug substance GMPs' may give rise to a lot of exemptions which, in total, complicate the GMP text and dilute the purpose of having a clear framework. • The interpretation of the internationally implemented ICH Q7 guideline which is reflected currently in the EU GMP Part II must be retained and consistently reflected in the legal provisions related to APIs. • Many EU GMP Annexes per se are not applicable to drug substance manufacturing. For instance, many of the EU Annexes are very specific for sterile, bio products etc., Others like Annex 8, 15, 19, etc., are written with a clear focus /intent towards finished drug products.	

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Consultation item n° 2: Are there other aspects which should be considered? Please comment.		EFPIA is concerned about the level of detail that would be needed in 2003/94/EC to define 'exemptions' regarding API GMPs. For instance, among others the following aspects would need to be considered where differences between API and medicinal products occur are relevant: • Document retention times • Sample retain periods • Quality assurance system • Enforcement of companies to suppliers to implement GMPs at their facilities • Sterility assurance • Handling of products in transit • Complaint management • Recall procedure • Reuse, rework, reprocessing In summary, there are many specific elements where interpretation from medicinal product and drug substance perspective diverge.	
Consultation item n° 3: Do you consider this list complete? Please comment.		EFPIA strongly recommends to avoid ambiguity from definitions of 'starting material' which is • 'API-starting material' (i.e. raw material; see ICH Q7) and • Starting material' (i.e. APIs, excipients, see part 1 of the EU GMPs) Similarly, ambiguity exists for requirements regarding 'manufacturers'	

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		If an amendment to Directive 2003/94/EC is to proceed, in order to avoid ambiguity, then a wholly separate section in the Directive specific to Drug Substance would be less confusing. Any specific amendments of the articles that are considered to be necessary should be clear e.g. • Adjustments to *article 2* definition 5) and 6) in order to include active substances. • Active substances are concerned by the scope of *article 4* and this should be aligned with *article 2* • *Article 2* definition 5) should be aligned with *article 6 and 7* if needed • *Articles 4 / 9 /10 /11 & 13* should be listed in section 2.2	
Consultation item n° 4: Do you agree with this specific point? Do you consider that other provisions specific to active substances should be added?		See items before (in specific re item 1). *We recommend alignment of definition of 'API-Starting material' (i.e. raw material) vs. 'Starting material' (i.e. API/Excipients) across the regulatory and legal texts.*	
		EFPIA notes that the obligation on the API manufactures to verify origin of the API-starting materials might not be able to enforce for API manufacturers residing outside the EEA territory. As such we object to add such requirement.	

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Consultation item n° 5: Please comment on section 3. Please raise any other issues or add any other comments you wish to make which have not been addressed in the consultation items set out above.		There is no other issue at this moment.	

Please add more rows if needed.