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Comments to

THE CONCEPT PAPER SUBMITTED FOR PUBLIC CONSULTATION On the DELEGATED ACT ON THE PRINCIPLES AND GUIDELINES OF GOOD MANUFACTURING PRACTICE FOR ACTIVE SUBSTANCES IN MEDICINAL PRODUCTS FOR HUMAN USE (20 Jan 2012, Sanco.ddg1.d.6(2012)73176) – DEADLINE 20 APRIL 2012

Paragraph	Consultation Item No.	Question/Topic	Comment
Introduction			
			The European Generic medicines Association (EGA) welcomes the opportunity to comment on the EC concept paper on the delegated act on the principles and guidelines of GMP for APIs. Our key general remark is that the present Delegated Act should not create any new requirement which would introduce differences in the rules for API GMP which have been harmonised with other regions through ICH efforts (ICHQ7A).
1. Extension of the Directive on GMP for medicinal products to active substances			
	1		The EGA supports the principle of the extension of the scope of Directive 2003/94/EC to active substances as a means o to enhance coherence of the regulatory setting and o to emphasise the need for Good Manufacturing Practices (GMP) to apply to both medicinal products and active substances The approach to lay down the principles and guidelines of

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			GMP for active substances, medicinal products and investigational products in one directive seems reasonable as long as: The process does not lead to disharmony ot he EU GMP approach to API vis-a-vis that of other ICH regions and The particulars of active substances are carefully considered.
2. Adaptation of regulatory requirements of Directive 2003/94/EC to active substances			
	2	**Provisions in Directive 2003/94/EC that would not apply to active substances**	In the EGA's opinion, it is important to address specificities of medicinal products and actives substances in separate chapters, even if this triggers the repetition of some part of the text. We believe it would facilitate harmonised understanding and consequently enforcement by avoiding the definition of duties and responsibilities of API manufacturers and suppliers through exceptions to what applies to medicinal products manufacturers.
	3	**Provisions in Directive 2003/94/EC that would need to be amended**	It is important that in addition to refer to the definition of active substance as introduced by the Directive 2011/62/EU, an explicit reference is made to specific situations such as atypical actives or active substances used in pharmaceutical development (laboratory work). We would recommend that these be either specifically excluded from the scope of this directive or referred to as exceptions and addressed for their specificities in annexes to the GMP guide. The directive should also provide clarification as to the non-applicability of importation requirements for those (as introduced in art 46b2). A reference to a definition for 'quality management (system)' preferably be envisaged.
			In addition to what has already been listed, the following items need to be amended:

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			• Art. 3 (2): "… published by the Commission in the 'Guide to good manufacturing for medicinal products, **for active substances** and for investigation medicinal products'. • It needs to be clear what is an active substance compared to an API starting material in order to avoid that all API starting materials could be considered active substances (particularly in the context of the new obligations on importation).
	4	**Other provisions on active substances that could be added to Directive 2003/94/EC**	Manufacturers of medicinal products already verify that API manufacturers comply with GMP and that only GMP compliant API is used in production (i.e. regular audits). Having a Directive on API GMP will not modify the above which is a cornerstone of the EU regulatory system. The EGA however supports the inclusion of clear obligations for API manufacturers as additional and complementing means to secure that only high quality API and medicines enter the legal supply chain. Such obligations on API manufacturers should focus on highlighting those essential elements which are needed for MAH and manufacturers of medicinal products to fulfill their own legal obligations. Examples of such essential elements are the provision of all necessary information required to fulfill the Qualified Person's declaration (art 8.3ha), to understand the API supply chain at stake (EU GMP guide – Chapter 5 – Production - ongoing revision) or the details of API outsourced activities (EU GMP guide – Chapter 7 – outsourced activities – ongoing revision) or the timely access to premises for audits. Point 16 certainly raises an important concern which has been

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			and is still debated in the EU (and elsewhere) for quite some time already without any harmonised conclusion so far. It is expected that ICH Q11 will bring more clarity in this context. The way point 16 is written seems to go beyond the mere scope of EU GMP for APIs (which apply from the moment the API starting material are used). The EGA is unsure of whether Directive 2003/94/EC is the adequate place to address this very specific matter. Should this point be kept in the final delegated act, we foresee a need: • to introduce a reference to the definition of 'API starting material' (Article 2) in the present context as it should not conflict with the GMP Guide definition (i.e. active substance and excipient, packaging material excluded) and, • to refer to the contractual link (quality agreement) an API manufacturer should have with his suppliers of API starting materials or intermediates. This could be referred to in a separate guidance document rather than in the Directive it-self. In light with the new requirements on API importation introduced by the Falsified medicines Directive, another obligation on API manufacturers would be that they ensure, where applicable, that active substances shall only be exported to the EU under the dual condition that ▪ EU importation rules are met (art 46b2) and; ▪ EU importers (the API recipients) are officially registered in the EU competent authorities registry (art 52a).
3. OTHER ISSUES			
	5	**Date of transposition of the delegated act** **Date of application of the delegated act**	The EGA does not have any specific comments as to the date of transposition or date of application of the delegated act

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		Any other issues or comments	given that the contents of the EU GMP Guide Part II (ICH Q7A) should not be affected by any of the articles, and as such the 'practice' should not be modified either. We would like to highlight here once more that the Delegated Act should not create any new requirement which would introduce differences in the rules for API GMP which have been harmonised with other regions through ICH efforts (ICHQ7A). OTHER comments 1) In Article 14 "Self-inspection", the revision of Directive 2003/94 provides an opportunity to align the text on the GMP guide "… and to propose any necessary corrective and/or preventive measures. Records shall be maintained of such self-inspection and any corrective and/or preventive action subsequently taken." 2) The revision of Directive 2003/94 provides another opportunity to align the text on the GMP guide There is a wording inconsistency throughout the directive that could be corrected now. While in the preface of this directive, the term "quality management system" is used, the further text speaks of a "quality assurance system". This should be changed in quality management (system) throughout the document in order to be in line with GMP and to avoid using different terms for the same thing. 3) In Art. 11 (4), the last sentence is dealing with the requirement of retention samples. It is important to clarify if this requirement will concern active substances and if retention samples of starting materials of active substances shall be retained. Alignment on the EU GMP Guide Part II is needed.

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			4) There are currently discussions around the Active Substance Master File (ASMF) assessment process in the EU and although it is premature to know what will change and when, we take this opportunity to point out that should ASMF worksharing become a reality, the directive might need to be amended in its article 5.2 to reflect the possible new paradigm through which the Marketing Authorisation Holder might no longer be the only concerned party in a position to apply for modifications.