Comments on the Concept Paper submitted for Public Consultation concerning the Delegated Act on Principles and Guidelines of Good Manufacturing Practice for Active Substances in Medicinal Products for Human use.
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Consultation Item	Comment / Rationale	Proposal
1 *"Do you agree with this appraisal and approach? Please comment"*	We agree that there should be a European Directive covering Active Substances, and that Member States should take appropriate measures to ensure that manufacturers of Active Substances on their territory comply with GMP for Active Substances. The Directive should take into account the appropriate differentiations, as determined through the delegated process. It appears from comments from our different members that it is not clear if EudraLex – Volume 4, Part II, would still apply to Active Substances as the "detailed guidelines". For example, we find the description for the extension of the EU directive to be somewhat contradictory. First, it is stated that separate guidelines exist for medicinal products and Active Substances (EudraLex – Volume 4, Part I and EudraLex – Volume 4, Part II, respectively.) The description then later states that, upon extension of the Directive 2003/94/EC, "the principles and guidelines for GMP would be the same for both medicinal products and active substances." The use of the term "principles and guidelines" makes it unclear if the intention is to suppress Part II of the GMP EudraLex-Volume 4. I**t should be made clear in the proposal that the "detailed guidelines" EudraLex-Volume 4, Part II, remains the valid GMP guidance for Active Substances, per recognition of ICH Q7.**	Each time reference is made to "detailed guidelines", we request that reference should be made to EudraLex – Volume 4, Part II.

2 *"Are there other aspects which should be considered? Please comment"*	We generally agree with the aspects which have been listed, and in particular, with the fact that the concept of Qualified Person and manufacturing authorization do not apply to Active Substances. However, it should be taken into account that any future modification to the current directive will need to be verified for its potential impact on Active Substances.	
3 *"Do you consider this list complete (amendments)? Please comment"*	Definitions should be harmonized with ICH Q7 and EudraLex – Volume 4, Part II The definition proposed for 'manufacturer' (art 46a (1) of Directive 2001/83/EC) is not appropriate. First, because the specific article cited is broader than that covering just a manufacturer, covering inter alia, also importers and distributors. Second, and more important, this article does not regard 'manufacturer[s of active substance], but regards the 'manufacturing of active substances used as a starting material'. This provision in fact came out before the Community Code even had a definition of "Active Substances", and was therefore utilized in connection with finished product registration requirements (in connection with Directive 2008/29/EC, by which it was added). It is recommended to add a definition for distributors who are not manufacturers. It is recommended to add a definition for 'starting material' to **Article 2** ("Definitions") to clarify starting materials. We consider "Active Substances" as they are defined in Eudralex Volume 4, Part II. We believe that the following sections of Dir 2003/94/EC should also be amended: **Article 2(5):** The term 'pharmaceutical quality assurance" should be restricted to application to medicinal products manufacturing. **Article 3(2)**: It should be clarified that specific detailed guidance documents should be issued by commission concerning Active Substances. This would guarantee to keep in force the	Use the definition of 'manufacturing' set out in 1.1 of the EudraLex – Volume 4, Part II, which was specifically issued for dealing with GMP in Active Substances: "'manufacturing' includes all operations of receipt of materials, production, packaging, repackaging, labeling, relabeling, quality control, release, storage and distribution of active substances and the related controls". . **Article 2**, Definitions: "Starting material" means all the materials (e.g., excipients, active substances, etc.) which comprise a medicinal product. Other substances used for manufacturing the medicinal product, but which are not listed as a component of the medicinal product in the marketing authorization, such as solvents, are known as raw materials. **Article 2(5):** We suggest using the term "quality assurance". **Article 3(2)** should make reference to 'Guide to good manufacturing practice for medicinal products, for

	EudraLex Vol 4 part II. **Article 6**: refer to comments on Article 2. **Article 7(1)** refer to comments on Article 2. **Article 10(3)**: Provision for re-validation should not apply to active pharmaceutical ingredients, in reference to 12.60 of EudraLex Vol 4 Part II ("*Where no significant changes have been made to the system or process, and a quality review confirms that the system or process is consistently producing material meeting its specification, there is normally no need for revalidation*"). **Article 11(4)**: Refer to suggested definition on starting materials.	Active Substances and for investigational medicinal products' Add to **Article 10(3)** a statement according to Eudralex Vol 4 Part II, 12.60
4 *"Do you agree with this specific point (starting material)? Do you consider that other provisions specific to active substances should be added?"*	In general, we don't agree with the addition of articles in the Directive each time there is a concern related to falsified medicines. We don't agree with the specific point on starting materials. This is already covered in EudraLex Vol.4 part II and part of the supplier qualification and change control.	

5 *"Please comment on section 3 (dates).* *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"*	**Comments on implementation and application date:** If no new requirements are introduced as compared to ICH Q7 and Eudralex Volume 4, Part II, and the requirements are clearly communicated, then we consider the proposed timelines as being acceptable. So far, all delegated acts in force took the form of regulation. This ensures direct application by all member states and simplifies implementation of the measure. We would recommend that the delegated act should take the form of regulation. **Other Comments:** Currently an inspection of Active Substance producers by the competent authorities is not a pre-requisite in the European system; instead it is the responsibility of the manufacturing authorization holder to ensure the Active Substance supplier/ manufacturer's GMP compliance by performing regular audits. The FMD and – as a consequence any delegated act as well – covers medicines for *human* use only. The detailed guidelines for GMPs for Active Substances (Eudralex Vol 4 Part II), however, cover both Active Substances for human and veterinary use.	We recommend that the responsibility be on the competent authorities. In order to prevent imbalance, we recommend that any modification of Directive 2003/94/EC related to GMPs for Active Substances for human use should also apply to Active Substances for veterinary products, by parallel or subsequent amendment of Directive 91/412/EC.