Dear Sirs,

Please find LEO Pharma's comments below.

ADMINISTRATIVE CHANGES

- A4: Sentence is becoming really complicated. Consider to split into different sub-categories even though they are all the same class (IA)

- A4, A5, A7: Consider to specify also stability testing site

- A7a: States "site where batch control takes place". This is inconsistent with A4 etc. where the terminology is "**quality control testing sites"**

- A7b: This case seems very specific and really nothing one would expect to find in the guideline. We would assume that a case like this is filed in active agreement with the RMS. It also feels a bit contradictory to its own Condition 2… Why would one delete a site just because they are up for an inspection if it is expected that they will pass?

DRUG SUBSTANCE

- **B.I.a.1:** Consider to specify also stability testing site

- **B.I.a.1: Condition 2 states "**The active substance is not a biological/immunological substance or sterile.". Considering that it might very well be so that different sites are used for chemical processing and the sterilisation operation, it would be sound to change condition 2 to **"**The active substance is not a biological/immunological substance.". and add a condition "For sterile substances: The manufacturing site is not involved in the sterilisation operations". This condition can be used to process changes to pure chemical processing sites in a common way and to process changes involved in sterilisation in a more comprehensive way

- **B.I.b.1:** Add a category for **Introduction of skip-lot testing of a specification parameter (IB)**

- B.I.d.1c): Should use CTD terminology: stability protocol = post-approval stability protocol. This change is considered important but it does not seem to fit under the heading of B.1.d.1. Consider own category

- B.I.f.1: Documentation requirements are odd. Suggest 1 and 2 to be merged "post approval change management protocol including a detailed description of the proposed change to be managed under the protocol". Regarding requirement No. 3: An amended dossier is submitted first when the actual change is submitted, as outlined in the approved CMP (**B.I.f.4)** or does this mean that it is required to send in drafts of revised CTD Modules with the proposed CMP?

- **B.I.f.3: For clarity documentation should state: Revised** post approval change management protocol

DRUG PRODUCT

- **B.II.b.1: Consider to add "Site for storage of the drug product (before batch release)". Should be Type IA_{IN}. As it is today you are forced into a IB under f). This is a situation where you use a contractor warehouse. Also consider to add stability testing site**

- B.II.b.1: Regarding the QP Declaration: It is proposed that a link to the preferred EU template to this document is added to Eudralex Vol. 2C. Experience is that for national products, there are different specific requests on the content of these declarations. Such requests would be less frequent if it is clear the it is a standard EU template. This comment is generic.

- **B.II.d.1:** Add a category for **Introduction of skip-lot testing of a specification parameter (IB)**

- **B.II.e.1: Difference between a) and b) is not clear. If one moves from e.g. a plastic bottle to a laminated tube for a semi-solid, this would fall under b)1 but is there then also a need to file an a)2? To clarify this, it is suggested to amend the title of a) to be" Qualitative and quantitative composition *while maintaining the packaging type*".**

• □ □ □ □**B.II.f.1: e)** Should use CTD terminology: stability protocol = post-approval stability protocol . This change is important but it does not seem to fit under the heading of B.II.f.I. Consider own category

• □ □ □ □**B.II.h.1: see** B.I.f.1:

• □ □ □ □B.III.1: a.1) This is the category that is used when replacing a previous section 3.2.S or an ASMF with a CEP. However this is not very clear from the title. Suggest to rename category to "Replacement of full CTD section 3.2.S/ASMF with a CEP from an already approved manufacturer"

Yours sincerely,

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