19 March 2018

Transparency Register number: 38526121292-88

Submission of comments on Revision of 'Annex 1: Manufacture of Sterile Medicinal Products'

Comments from:

Name of organisation or individual
EFPIA – Silvia Garcia (silvia.garcia@efpia.eu)

1. General comments

EFPIA welcomes the Revision of Annex 1 (Manufacturing of Sterile Medicinal Products) and would like to bring the following high level key comments to the attention of the EU regulators and inspectors.

General Points

Overall Impact

The introduction of several new requirements will have an impact on sterile manufacturing operations whereas the 2015 Concept Paper (EMA/INS/GMP/735037/2014 – section 6), indicated that "No adverse impact on industry with respect to either resources or costs is foreseen, although clarification of the use of new systems may lead to the requirement for some facilities, equipment and processes to be modified over a period of time." These new requirements include for example the introduction of:

- Requalification of grades A & B areas every 6 months
- HEPA/ULPA filters in all classified areas, including Grade D
- Contamination Control Strategy
- A qualification list for material airlocks leading to grade A and B.

Scope

Reference to application of "some principles and guidance" to non-sterile product manufacturing should be avoided, i.e. Annex 1 should be restricted to manufacturing of sterile product in order to avoid any confusion with applicable regulatory requirements for non-sterile medicinal products (including Biotech-API upstream process) and misinterpretation during inspection of facilities. For instance, if a company only manufactures non-sterile medicinal products, they will not refer to a sterile manufacturing annex.

Regulatory Co-Sponsorship

The co-sponsorship of the annex with PIC/S and WHO is welcomed, as will help the industry and inspectors worldwide to move closer to global harmonisation standards and expectations with respect to sterile manufacturing.

Implementation Transition

The implementation time will be critically dependent on the final wording of the Annex 1. In any case, significant time will be required for manufacturers and inspectors to become aligned with interpretations of the text, and for manufacturers to update their Quality systems and processes accordingly. The necessary capital investment should not be underestimated either. Industry and Inspectors may benefit from an implementation training or workshop to help align any interpretation.

As the implementation of new requirements would require substantial changes of process and practices, the European Commission should foresee a minimum 24 month transition period during which the manufacturer could perform gap assessments and define action plans to meet the revised regulations.

Specific comments on text

Technical Points
Technical Parameters We welcome the additional detailed wording that supports certain specific technical parameters to be used which significantly reduces interpretation (e.g. section 5.3:Grade A zone airspeed measurement). However there are still some specific parameters (e.g. requalification of grades A & B areas every 6 months) which are more restrictive than before and not aligned with ISO-14644. Thus we propose that those parameters be reviewed.
Quality Risk Management (QRM) We welcome the inclusion of QRM principle in the document, and suggest that prescriptive requirements be reviewed and reduced, so that the use of QRM principles in that context is facilitated. Also certain prescriptive requirements are not complete or even inaccurate. (e.g. environmental monitoring). Some areas where QRM would prove most useful to the user have been mandated and do not appear to permit the use of QRM such as; • Section 5.29 –"*Clean rooms should be requalified periodically and after changes to equipment, facility or processes based on the principles of QRM. For grade A and B zones, the maximum time interval for requalification is 6 months".* This is more restrictive than before and not aligned with ISO-14644 without an opportunity to apply QRM principles to go beyond 6 months • Section 8.106 - "*The lyophiliser should be sterilized before each load"*. In our opinion the frequency for sterilization of lyophilised units should be risk based depending upon the equipment and process (e.g. Frequency of sterilisation of could be based on QRM when using a fully closed isolator and automated loading). • Section 8.84 - *"The integrity of the sterilized filter assembly should be verified by testing before use, in case of damage and loss of integrity caused by processing, and should be verified by on line testing immediately after use by an appropriate method such as a bubble point, diffusive flow, water intrusion or pressure hold test. It is recognised that for small batch sizes, this may not be possible; in these cases an alternative approach may be taken as long as a formal risk assessment has been performed and compliance is achieved".* The use of pre-filtration integrity testing may in some specific cases actually increase the risk of non-sterile product due to the technology and manipulations required whatever the batch size. Another example: we acknowledge that the validation requirements are aimed for any commercial products being manufactured, and that only some aspects of validation are applicable at each phase of development. Thus, the validation section of the Annex should specify that Investigational Medicinal Products manufacturers should apply QRM principles to clearly define validation expectations for each phase of clinical development.
Design and Technology It appears that there is a propensity within the document towards an overall emphasis on quality control and testing rather than design, validation and sterility assurance programs. This will add operational complexity, reduction of production capacity, with the potential for

additional operational risks and cost.

For instance, the controls outlined are universal regardless of the technology (e.g. isolator, RABS). Many of the controls involve taking operations off-line limiting the time available for manufacture of product for supply. In addition, some of the controls are invasive and may have the unintended consequence of adding risk.

Also, the document detailed requirements are based on current technology and prescriptive in detailed methodologies. This could contradict the basic principle to promote modern technologies (scientific, engineering and analytical methods) as manufacturers will be limited in new technology, testing and assurance options for many years to come.

Contamination Control Strategy

We welcome the concept of a Contamination Control Strategy to demonstrate our holistic approach for sterile manufacturing, and we believe that each manufacturer should decide on how to include in their Quality Management System. Furthermore, this may take more than 12 months to implement, as the necessary documentation would have to be developed for each processing facility including relevant contract manufacturers.

Terminology

We believe that the document should be reviewed for consistency of definitions and meaning of terms. For instance, "cleaning process, sanitization, disinfection, sterilization / in sterile state"

The use of 'must' and 'should' should be consistent. For instance, instead of "Investigations *should* be performed into non-conformities, such as sterility test failures" "Investigations *must*….." is more appropriate.

To avoid that the term 'should' is over-interpreted as 'must' during inspections from different international regulatory authorities, it is suggested that this is clarified during any training related to annex 1.