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RE: Second Consultation of the Draft Annex 1 Revision

Dear Mr. Gross and Ms. Moseley,

This is a letter from the joint group of industry associations that is being sent separately from the submission of each association's individual comments.

On February 19, 2020, notice was sent by the European Commission to industry associations requesting a second targeted consultation of version 12 of the draft Annex 1 revision. In response, the undersigned industry associations will be submitting their comments, recommendations on changes, and the justification for changes to the Annex. Each association established and followed their own procedures for soliciting, considering, and submitting specific comments from their respective membership. Although, each association's set of comments represents a different segment of the industry and geographic area, the association representatives see value in communicating some important common points uncovered during the Annex 1 revision process.

1. ***The Annex should be flexible to support the use of appropriate alternative approaches.*** It is important that where alternative approaches are supported by appropriate rationale and risk assessment and meet the intent of the Annex, that these alternative approaches be considered as acceptable. Regulators should allow flexibility to implement alternative process control strategies that effectively support product supply and patient (human and animal) needs, while meeting *the underlying intent of the* Annex for uncompromised product quality and safety principles. The importance of emphasizing in the Annex that adequate alternative approaches based on quality risk

management (QRM) are acceptable and may even be indispensable to achieve the intent of the Annex cannot be overstated.

This is the time for the industry and regulators to embrace contamination control strategies (CCS) based on QRM principles. The adoption of Quality by Design principles and risked based strategies for the attainment of quality and the prevention of failure is ever more important as an alternative to the traditional reliance on detection, monitoring and testing. Today the quantity and quality of scientific knowledge is much higher and widely spread than in the past. These control strategies must not only fit quality and supply needs, but as implied in EU Directives 2001/83/EC article 23 and Directive 2001/82/EC Article 27, be flexible enough to be of use today and to support the use of new technology, approaches, and therapies, both anticipated and unanticipated in the years that follow. If we fail to do this, then the increasing speed of learning and technology advancement will outpace our ability to take advantage of these advancements in a timely and effective manner.

2. ***There must be clear interpretation of the Annex.*** It is essential that all who use and depend on this document have a clear and single interpretation of its meaning and intent. While the Annex is a European guidance, the Annex includes input from and will be used also by PIC/S and WHO. As such, it represents the latest scientific discussion of sterile product manufacturing and control and will be viewed as a global guide for the appropriate planning and design of such processes. To achieve the needed level of clarity, three important points should be considered:

    - The use of specific examples should be avoided, because no matter how well they are defined as "examples", they will be misinterpreted as rigid requirements by some in industry and some inspectorates. Without such clarity, there is a risk that companies will be discouraged from using innovative, alternative approaches.

    - Clear distinctions between similar but different technologies and approaches, including isolators and RABS, form-fill-seal and blow-fill-seal, liquid and hard goods moist heat sterilization, and environmental qualification and classification are needed to understand the benefit and limitations of the respective technologies and promote their most effective use within the contamination control strategy. Without such clarity, there is a risk that companies will apply inappropriate control strategies.

    - An over-emphasis on process testing and monitoring (e.g. PUPSIT and APS) should be avoided, and instead, effective reliance on well-designed process and process control design and performance should be encouraged. Without such balanced approach, there is a risk that companies and regulators will apply a rigid interpretation and miss the opportunity to use process design to prevent failures, relying instead on the testing and monitoring to detect failures.

This should be a partnership between regulators and manufacturers. Ensuring and improving sterile healthcare product quality, safety and effectiveness as well as supply availability can only be attained and maintained through a partnership of the manufacturing sector and the health authorities. History and recent events, including the challenges uncovered by the pandemic, have shown that this partnership is essential. Rapidly evolving technology and the importance to accelerate the development and availability of medicines to treat unmet medical needs of patients worldwide require the cooperation of experts from the industry, academia and regulatory agencies.

3. ***More work is needed.*** We recognize that additional efforts will enhance the effectiveness of the Annex. These include the three key considerations: While much of the Annex covers topics where there is adequate scientific knowledge and consensus to clearly present positions, there are other topics which require additional scientific work to determine the most feasible and effective approaches. In these cases, a continued dialogue between regulators, industry, and academia to further develop guidance that is aligned with advances in knowledge and technology is of outmost importance. In addition, after Annex 1 has been finalized and made operational, there will inevitably be differences in the interpretation of specific sections of the Annex by regulators and/or industry. A mechanism to discuss and resolve such differences collaboratively in a joint regulator/industry forum or committee would be beneficial for everyone, with the outcomes published by the regulatory authorities as interpretive guidance or Q&As. Finally, the effective implementation of this revised Annex will involve a significant effort to educate industry and regulators on proper intention and use the CCS and QRM principles that form its basis. The associations offer their assistance to help with that effort, through coordinated workshops, meetings, and training.

The undersigned associations have worked in a spirit of cooperation, continuing the efforts of the inter-association working groups to assisting the EMA and PIC/S with the gathering, analysis and communication of input from the sterile healthcare community and offer to work with the EMA to further the development of the guidance.

There is consensus among the associations that this Annex represents a great opportunity to improve the understanding of process control in our industry. As the EMA noted in its 2015 Annex 1 revision concept paper, a key objective of this revision is to *"embrace the use of new technologies to prevent detrimental impact on product and to encourage the introduction of new technologies that are not currently covered."* The points noted in this letter, along with the individual comments of the associations are meant to help the EMA and PIC/S meet this common objective for clearly defined, modern guidance on contamination control strategies based on scientific evidence and quality risk management principles that promote technological and sterility assurance advancement for many years to come.

Yours sincerely, on behalf of A3P, AnimalhealthEurope, AESGP, ECA, EFPIA, EIPG, EQPA, ISPE, Medicines for Europe, PDA, PHSS, and Vaccines Europe.

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