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Radhakrishna S Tirumalai
USP Compendial Science
12601 Twinbrook Parkway
Rockville, MD 20852

Re: USP Stimuli Article "Sterility by Design for Sterile Drug Products"

Dear Dr. Tirumalai,

PDA appreciates the opportunity to provide feedback on foundational concepts for our industry such as the USP *Sterility by Design for Sterile Products* stimuli article that will be utilized to develop future approaches and requirements in updated USP monographs and chapters.

In addition to specific detail comments enclosed, we would like to highlight some key points for your consideration here:

1. Continued recognition of the use of the sterility test with moist heat terminal sterilization processes

It is well known and universally accepted that sterilization processes are considered to be "special processes" whereby the results of these processes, including achievement of sterility, cannot be confidently confirmed by testing. Despite this understanding, the global sterilization community continues to be unnecessarily reliant on the test for sterility to support the disposition of sterile products. Parametric release programs which obviate the need for the sterility have been in use with products terminally sterilized by moist heat for nearly 40 years. However, parametric release has not been fully embraced in the US or other countries and regions where supporting regulation is fully available to support its implementation. A stronger position as expressed in our comments on this topic would have a favorable effect on the adoption of parametric release in the US and across the globe.

2. Use of parametric release principles with aseptic processing

Most (if not all) of the recognized flaws and limitations of the sterility test are equally applicable to its application to aseptic processing. The principles of parametric release are well-described in USP and in other global guidances and standards for products terminally sterilized with moist heat, but there is not a strong connection of these principles to aseptic processing. As we consider future opportunities for the advancement of aseptic processing, the application of the principles of parametric release to this modality should be recognized and fully embraced to drive the initiation of discussion on the sterile release of aseptic products without any reliance on the sterility test. Similarly, incremental and effective mitigation of contamination risks during aseptic processing could be achieved through the use of post aseptic processing lethal treatment (not sterilization) processes that employ milder treatment conditions on product than traditional sterilization processes.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in the pharmaceutical manufacturing of sterile products and pharmacopeia publications on behalf of PDA's Science Advisory Board and Board of Directors.

If there are any questions, please do not hesitate to contact me.

Sincerely,

Richard Johnson
President, PDA
Cc: Glenn Wright, Josh Eaton

PDA Comments

USP *Sterility by Design for Sterile Products* stimuli article published March 1, 2022

	Section	Reference Text	Comment to Specific Text	PDA Recommendations
1	Aseptic Processing	"Recent general informational chapters added to the US Pharmacopeia on sterility assurance have correctly shifted the emphasis in aseptic processing from monitoring (environmental sampling, media fills, and sterility testing) to a Sterility by Design model (7–8)."	The "Sterility by Design" model should be linked to the proposed EU Annex 1 requirement for the use of Quality Risk Management (QRM) and a holistic Contamination Control Strategy (CCS), as design is one of the most important aspects of sterility assurance. The final Annex 1 revision is expected to publish within the next few months, and these are central themes of the document.	PDA recommends the incorporation of the principles of Quality Risk Management (QRM) and Contamination Control Strategy (CCS) into the revision. QRM to ensure prevention of microbiological ingress into the final drug product. Contamination Control Strategy (CCS) to ensure identification of critical control points and the proper design, assessment, and review of contamination controls.
2	Aseptic Processing	Under “Aseptic Processing”, it states “When more than 99% of samples taken in critical environments are sterile, and media fills routinely have no contaminated units, the sterility test becomes largely ceremonial…”.	It’s not clear what it meant by “samples taken in critical environments are sterile”. If this is in reference to environmental samples the term “contamination recovery rate” should be used to maintain consistency with USP <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments*. It would be helpful to ensure linkage to EU Annex 1 concepts and requirements for the use of Quality Risk Management (QRM) and a holistic Contamination Control Strategy (CCS), as design is one of the most important aspects of sterility assurance.	PDA recommends that the meaning of "samples taken in critical environments are sterile" be clarified. While environmental and utility monitoring are important, these are not controls, but measures (i.e., on-going evaluation) of the manufacturing controls built through proper facility and system design based on QRM principals. Aseptic Process Simulations (i.e., media fills) are an evaluation of all the controls built through proper facility design, process develop and product capability; therefore, APS are similar to EM, as they are only evaluating all systems when combined to provide a 'snap-shot' of the holistic contamination control strategy. This needs to be clearly outlined in any revisions to USP chapters driven by this stimuli document.

3	Figure 1	Label on Y-Axis of Figure 1: "Increased Separation of Personnel"	The label on the Y-Axis of Figure 1 is incomplete as it need to include the term "Product". While the graph does provide a good representation of the increase separation between personnel and the process it alone cannot be the differentiation factor in increasing sterility assurance. The way in which any piece of equipment or barrier system is used will have an impact on the "Confidence in Sterility Assurance". It is important that any such figure convey this point as the use of a barrier, if not properly designed, used and maintained, can create a decrease in the level of "Confidence in Sterility Assurance" as compared to other process that have less separation between the Personnel and Product. Separation of personnel alone is not the primary driver of relative confidence in sterility assurance.	Change Label on Y-Axis to: "Increased Separation Between Personnel and Product" Ensure the text associated with the figure or text within the figure conveys that the use of Barrier systems alone cannot Increase the Confidence in Sterility Assurance unless they are properly designed, used and maintained.
4	Figure 1	Placement of Open RABS at an increased level of separation of personnel and increased confidence of Sterility Assurance than Barrier System	This is an area where clear definitions and examples of the terms "Barrier System" and "Open RABS" and "Closed RABS" would be beneficial based on the varied use of the terms today. It would also be helpful to differentiate between each and its location on Figure 1.	PDA Recommends adding definitions, narratives, and examples to provide clear differentiation of all barrier category terms to support the location of each in Figure 1.

5	Recommended Changes to Existing Chapters	Elimination of the separate section on Post-Aseptic Terminal Sterilization within Table 1 due to it being redundant and overly restrictive.	The term Post Aseptic Terminal Sterilization is redundant as terminal sterilization is already well-covered by various existing USP chapters and this approach can easily be applied to products that were previously manufactured via aseptic processing. However, it is recommended to recognize and develop future content to support the application of Post Aseptic Lethal Treatment as this encompasses "milder" non-sterilization treatment options with low doses of radiation or at temperatures below traditional heat sterilization temperatures. Please note that this process type is also recognized in 8.3.3. of EU Annex 1 Revision 12 and discussed in the EMA guidance document “Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container”	PDA recommends development of content in USP to support Post Aseptic Processing Lethal Treatment.
6	Recommended Changes to Existing Chapters	There is currently no content in the chapter <1229> series that describes the sterile product release mechanism that should be utilized for porous hard goods load items (e.g., containers, closures, aseptic supplies/equipment/parts, etc.).	The stimulus article does not include the chapter <1229> series as also needing revision. There is a no content in the chapter <1229> series that describes the sterile product release mechanism that should be used for medical devices or load items used in aseptic processing that are sterilized with direct contact. Although these are not final products in the same realm as medical devices, the sterility of load items used in aseptic processing is critical to the assurance of sterility these products.	PDA recommends that the following statement be added to the Routine Process Control section of <1229.1>: "The principles of parametric release <1222> can be utilized to support the sterile product release of load items sterilized by direct contact."
7	Recommended Changes to Existing Chapter	There is currently no content in chapter <1222> that describes the approach that should be utilized for parametric release of products manufactured in closed isolators or closed systems.	The stimuli article does not include chapter <1222> as also needing revision. Currently chapter <1222> does not, but should, include content that describes the approach to be utilized for parametric release of products manufactured in closed isolators or closed systems.	In order to support footnote “d” from Table 2, PDA recommends that scientifically valid CFR-compliant content (similar to the content currently provided for products terminally sterilized with moist heat) be added to chapter <1222> that describes the approach that should be utilized for the parametric release of aseptically processed products manufactured with BFS/FFS, closed isolators or closed systems.

8	Table 1	References to CNC in Table 1	Table 1 references the FDA's 2004 AP guidance regarding a CNC environment for open and closed isolators. Appendix 1.B.4. of the guidance states that "An aseptic processing isolator should not be located in an unclassified room" so an ISO 8/Grade C environment is expected by the FDA for any isolator used for aseptic processing operations. Table 2 states that an ISO 8 environment is to be used as a background for open and closed isolators the Table 1 reference to the acceptability of CNC backgrounds for isolators may be an error.	PDA recommends removal of the CNC from background environments permitted with open and closed isolators for agreement with the background environment listed in table 2 and Appendix 1.B.4 of the FDA's aseptic processing guidance.
9	Table 2 # of Media Fill Initial/Annual Column	# of Media Fill Initial/Annual	1) Future chapter content should reflect that aseptic process simulations should be of sufficient durations to capture and address duration-affected process variables that pose risk to product sterility, but that there is otherwise no scientific basis to requiring that aseptic process simulations: -be performed at full process duration -be used to establish or qualify maximum process duration -be used to establish or qualify maximum product or process holding times -be used to establish or qualify the maximum length of time operators or people can be in the clean room or the impact of operator fatigue on the aseptic process. 2) Future chapter content should reflect that process interventions should be designed and qualified such that these can be successfully performed by any properly qualified clean room operator or individual and that the aseptic process simulation does not validate or qualify the intervention, does not establish or qualify the frequency or number of times an intervention may be performed during production, and alone does not qualify the individual performing the intervention.	It is important that industry and scientific publications continue to counter the scientifically invalid and increasing regulatory supported position that all aseptic process simulations must be performed at full duration and all interventions must be performed by all aseptic processing personnel at the same frequency as these are performed in production. This position has a severely limiting effect on productivity of modern aseptic processes, especially those used to manufacture ATMP products. It would be valuable to industry if guidance on the duration of APS and frequency of interventions could be provided including details and criteria that should be used to set intervention frequency for a given technology. It should be highlighted that it's up to each company to assess APS duration. Additionally, content on these and other aseptic processing topics should be aligned with industry association positions on these topics including PDA TR No. 22 which is under update, PDA Points to Consider Documents and others.

10	Table 2 Manual A/P Cell	Manual A/P Row	Need to address the different considerations related to conventional manual fill and the manual aseptic manipulations associated with new technologies such as cell and gene therapy (ATMPs). The absence of a distinction between manual aseptic filling and manual aseptic manipulation can restrict the manufacturing and availability of ATMP products by imposing the need for controls that have limited value.	PDA Recommends the row that covers Manual Aseptic filling should be split into two categories: Manual Aseptic Filling and Manual Aseptic Manipulations and populated accordingly.
11	Table 2 Footnotes	Foreground Environments [a] Foreground environments are ISO 5 areas where sterilized materials, products, and primary packaging components are exposed. Background Environments [b.] Environments adjacent to foreground environments.	The Environment Foreground/ Background details in Table 2 are excessively burdensome for some applications. For example, the background for Open RABS is not always ISO 5 and for ATMP's, ISO 5 is not used with closed systems. To avoid confusion and to allow the proper Foreground and Background environments to be classified correctly the following changes should be made to the description and the area Environmental Classification in Table 2 reset based on these changes. For clarity and to avoid misinterpretations the description of Foreground Environments should be modified to clearly communicate that the items are openly exposed with no protective sealed covering or overwraps in place, "…and primary packaging components are openly exposed with no protective sealed covering or overwraps in place." For clarity and to avoid misinterpretations the Background Environments description should be modified to clearly indicate that in these environments the sterilized materials, products, and primary packaging components are not exposed being in closed vessels or other containers with protective sealed coverings/overwraps in place to maintain their sterility, "Environments adjacent to foreground Environments where sterilized materials, products, and primary packaging components are not exposed, being in closed vessels or other containers with protective sealed coverings/overwraps in place."	Please update Table 2 accordingly

			Based on these clarified descriptions the current Table 2 Foreground/Background recommendations for Manned Conventional/Open RABS, ISO 5/ISO 5 and Closed RABS, ISO 5/ISO6 would be excessively burdensome and should be changed to align with the current industry accepted approach that utilizes an ISO 5-7 background for conventional rooms based on design.	
12	Sterility Tests <71>	The following changes are suggested for this chapter: -Acknowledgement that parametric release should be the default mechanism for product release subsequent to a validated terminal sterilization process. -Inclusion of explanatory content that reflects the change in perspective reducing the importance of sterility tests.	The continued use of the term "default" in this instance is confusing as the sterility test remains an acceptable alternative option to parametric release. As currently written, this may be interpreted as being in conflict with the intended position on the sterility test. If there are specific applications where the sterility test can be used as a scientifically valid alternate to parametric release, these examples should be provided and fully described. Any content related to the application of the sterility test to aseptic processes should provide cautionary statements highlighting its limitations and the risks of overreliance. Additionally, the principles of parametric release from <1222> and other global guidances and standards be recognized to strengthen the assurance of sterility with aseptic processes.	PDA recommends the following changes for this chapter: -Acknowledgement that parametric release should be the ~~**default**~~ mechanism for product release subsequent to a validated terminal sterilization process -Inclusion of explanatory content that clearly describes the specific scenarios (if any can be identified) for which the application of the sterility test is acceptable/scientifically valid; otherwise, it should be stated that there is no valid alternative to parametric release -Development of a section that outlines the requirements and situations where the principles of parametric release can be applied to products produced by aseptic processing.
13	Table 2 Footnote	Terminal Sterilization [d] Parametric release is the default for these production methods.	Footnote “d” in Table 2 on terminal sterilization is missing “sterile products”. As the table is focused on sterile products, and based on comment 12 above, the text should read “Parametric release is the sterile product release mechanism for these production methods.”	PDA recommends the following change for this footnote: “Parametric release is the sterile product release mechanism for these production methods.”