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Huiping Tu
12601 Twinbrook Parkway
Rockville, MD 20852-1790, USA

Reference to Correspondence Number – C326603

Proposed <1071> Rapid Microbiological Methods for the Detection of Contamination in Short-Life Products — A Risk-Based Approach– USP PF 46(6)

Dear Dr. Tu:

PDA is pleased to have the opportunity to provide comments on the proposed USP Informational Chapter <1071>, released for public comment on January 2, 2024. We recognize that the purpose of the proposed chapter is to provide guidance on the developing a risk-based approach to release of sterile short-life products using rapid microbial tests.

Our comments were prepared by an international group of expert volunteers with experience in cell and gene therapy product regulation, development, and manufacture specifically related to microbiological testing. These comments were prepared on behalf of PDA's Advanced Therapy Medicinal Products Advisory Board and provide some overall points with respect to the proposed chapter, as well as a number of specific technical comments. The specific technical comments are organized by the draft's section headings.

PDA is a non-profit, international, professional association of more than 10,000 individual industry members having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality.

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

Sincerely,

Glenn Wright
President, PDA

CC: Joshua Eaton, PDA

General Comments
The title of the General Information Chapter is unclear what the scope is intended to be. Is the revised chapter meant to be used for release of sterile products, by way of a sterility test, or some bioburden assay?

Specific Comments to the Text			
Section	**Current Text**	**Proposed Change**	**Rationale**
SAMPLE SIZE CONSIDERATION	Entire section	Delete this entire section and provide guidance on sample size considerations (1% rule, similar to Ph. Eur. 2.6.27).	It is unclear as to the relevance of this entire section for determining how much sample to use for a sterility test. The section offers no practical information on how to use the formula. For example, how would one know what the number of CFU is in the total product volume?
USER REQUIREMENT SPECIFICATIONS FOR A RAPID MICROBIOLOGICAL METHOD FOR THE DETECTION OF CONTAMINATION IN SHORT-LIFE PRODUCTS	Low rates of false positive results. False negative rate not worse than ⟨71⟩ if the system is used as a release sterility test or low rate of false negative results if the system is used in a risk-based approach (e.g., LOD > 1 CFU but faster results are more beneficial).	There should be no false positives. The rapid method should be comparable or non-inferior to the existing method.	Defining equivalency of an Advanced Microbiological Method as not worse than <71> in terms of recovery and false positive rate is not consistent with the USP General Notices and <1223> where the acceptance standard is defined as comparable. There should be no false positives. How would you demonstrate false negative rates; simply show comparability or noninferiority to the existing method.
Brief Descriptions of the Example Technologies	[no mention of alternate technologies]	The chapter should address emerging and future technologies as long as the sponsor determines it meets the URS and ensures patient safety.	The chapter should not exclude appropriate technologies for use
Brief Descriptions of the Example Technologies	[no mention of flow cytometry]	Address flow cytometry as a current technology.	Flow cytometry is an appropriate rapid method to consideration.

Specific Comments to the Text			
Section	**Current Text**	**Proposed Change**	**Rationale**
METHOD VALIDATION AND SUITABILITY TESTING	It is recommended to perform the method suitability testing on three different lots, or three independent runs if three lots are not available.	Provide an alternative strategy in the event the material is not available.	Sufficient investigational material or drug substance may not be available to perform this testing on three lots or runs. For example, in early pharmaceutical development firms typically use donor apheresis material for method qualification.
METHOD VALIDATION AND SUITABILITY TESTING	The detection of the challenge organisms in the presence of product must be demonstrated.	Addition of guidance on the selection of microorganisms.	There is currently no direction on specificity.
METHOD VALIDATION AND SUITABILITY TESTING	…the results from testing actual samples may give results that are not equivalent to that using other technologies.	Need to better clarify what this statement means with examples.	The current statement is confusing to the reader and offers no benefit without further clarification.