PDA Global Headquarters
Bethesda Towers,
Suite 600
4350 East West Highway
Bethesda, MD 20814 USA
TEL: +1 (301) 656-5900
FAX: +1 (301) 986-0296

PDA Europe gGmbH
Am Borsigturm 60
13507 Berlin
Germany

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

Reference to Correspondence Number – C326604
Proposed <72> Respiration-Based Microbiological Methods for the Detection of Contamination in Short-Life Products – USP PF 46(6)

Dear Dr. Tu:

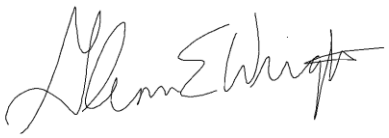
PDA is pleased to have the opportunity to provide comments on the proposed USP Chapter <72>, released for public comment on January 2, 2024. We recognize that the purpose of the proposed chapter is to provide guidance on the developing microbial detection assay methods based on ATP bioluminescence.

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
PDA recommends further reconciliation and alignment between expectations and methodologies presented in USP Chapters <72> and <73>, especially in terms of defining the growth promotion and method suitability challenge organisms as related to the certified reference strains found in <71>.

Specific Comments to the Text			
Section	**Current Text**	**Proposed Change**	**Rationale**
BRIEFING	local isolates should be considered with appropriate risk-based justification	PDA recommends modifying the text to: "local isolates **may** be considered with appropriate risk-based justification"	This presents using local isolates as an optional activity rather than required.
CULTURE MEDIA AND INCUBATION CONDITIONS	The choice of media should be risk-based and consider the temperature and degree of exposure of oxygen used during the manufacturing process.	PDA recommends providing more guidance on the "degree of exposure of oxygen" to inform the user on media selection criteria.	The current text seems to have a theoretical definition of an oxygenated product. Could an anaerobic incubation be eliminated for a highly oxygenated product?
Growth Promotion Test of Aerobes, Anaerobes, and Fungi	Incubate for not more than 3 days in the case of bacteria or not more than 5 days in the case of fungi.	PDA recommends modifying the incubation time to reflect the results of method suitability studies.	The incubation time should reflect the minimum incubation time determined during method suitability.
METHOD SUITABILITY TEST	Entire section	PDA recommends the addition of minimum method suitability qualification requirements.	The current outline adds a safety factor but relies on the stakeholder to determine the appropriate organism to use and the generation time: not all users will have the expertise to do this. Additionally, there is a discordance between USP <72> and <73> method suitability test inoculum size (i.e., 10 versus 100 CFU) with the requirements in USP <60>, <61>, <62>, <72>, and the recommendations in <1223>.

Specific Comments to the Text			
Section	**Current Text**	**Proposed Change**	**Rationale**
DETERMINATION OF THE INCUBATION TIME OF THE PRODUCT TO BE EXAMINED	Entire section	PDA recommends simplifying the approach to incubation time determination (e.g., using a percentage of the longest time-to-detection).	The method presented is overly complicated alternative option could be a percentage of the longest time-to-detection.
DETERMINATION OF THE INCUBATION TIME OF THE PRODUCT TO BE EXAMINED	The incubation time for microbial detection in the product is calculated as follows: $T = t_{ttd} + \log_2(10) \times G$ …. The generation time (G) can be calculated as follows: $G = \frac{t}{3.3\ x\ log_{10}(\frac{N}{N_0})}$	PDA recommends the addition of reference sources for the origin and use of the equations if this section is retained.	References to the technical literature will aid in understanding the rationale and implementation of the two equations in the test chapter.
Table 1. Strains of Test Microorganisms Suitable for Use in the Growth Promotion Test	Table 1. Strains of Test Microorganisms Suitable for Use in the Growth Promotion Test	PDA recommends the addition of an asterisk to a reference stating 'these microorganisms are appropriate for use in method suitability determination, but the list is not comprehensive'	Manufacturers may choose to use different organisms based on recovery trends.
Table 1. Strains of Test Microorganisms Suitable for Use in the Growth Promotion Test	*Aspergillus brasiliensis* (formerly *A. niger*)	PDA recommends shortening the reference to: *Aspergillus brasiliensis*	*A. niger* has not been in common usage for an extended period of time and is no longer needed as a formerly-known-as reference
Volume of Articles to Be Tested	…the probability of detecting a contaminated unit should not be less than that for <71>.	PDA recommends clarifying this reference. Should this be a reference to <1071>?	USP <71> does not contain the referenced probability calculation.

Specific Comments to the Text			
Section	**Current Text**	**Proposed Change**	**Rationale**
Volume of Articles to Be Tested	A formula for calculating detection probability can be found in <1071>. Other statistical sample size calculations may be used, if scientifically justified.	PDA recommends including the calculation within the chapter text.	A test chapter should state what is an acceptable volume, not just refer to a calculation in another chapter.
Volume of Articles to Be Tested	Entire Section	PDA recommends defining the test sample size in alignment with other regulatory guidance, i.e., 1% of the total product volume rule or other appropriately determined volume.	The 1% of the total product volume rule, as outlined in Ph. Eur. 2.6.27 and USP <1072>, has obtained regulatory approval.
MONITORING AND INTERPRETATION OF RESULTS	Entire section	PDA recommends a reference to a risk assessment addressing equivalency to traditional compendial methods.	This would aid the end-user in situations including what to do with a non-CFU signal.
MONITORING AND INTERPRETATION OF RESULTS	(USP 1-Aug-2025)	(USP 1-Aug-202**4**)	Seems to be a typo regarding when this draft was last modified.