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March 28, 2024

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

Reference to Correspondence Number – C326605
Proposed <73> ATP Bioluminescence-Based Microbiological Methods for the Detection of Contamination in Short-Life Products – USP PF 50(1)

Dear Dr. Tu:

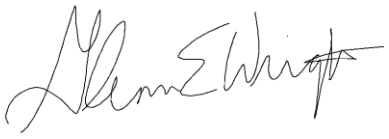
PDA is pleased to have the opportunity to provide comments on the proposed USP Chapter <73>, released for public comment on January 2, 2024. We recognize that the purpose of the proposed chapter is to provide guidance on the developing microbial detection assay methods based on ATP bioluminescence.

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**
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 modifying the text to: **The choice of media and incubation conditions should be risk-based in consideration of manufacturing process parameters (e.g., temperature, oxygenation level).**	The current text seems to limit the parameters to be considered during the risk-assessment.
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.

Specific Comments to the Text			
Section	**Current Text**	**Proposed Change**	**Rationale**
METHOD SUITABILITY TEST	The ATP bioluminescence-based method must demonstrate growth of the test microorganisms inoculated at not more than 10 CFU into the media containing the product.	PDA recommends modifying the text to: The ATP bioluminescence-based method must demonstrate growth of the test microorganisms inoculated at not more than **100** CFU into the media containing the product.	The method suitability test inoculum size, (i.e., <10 versus <100 CFU), does not align with the requirements in USP <60>, <61>, <62>, and <72> and the recommendations in <1223>.
Sampling Plans, Test Parameters, and Controls 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.