Advancing Transfusion and Cellular Therapies Worldwide

May 09, 2008

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

RE Docket FDA-2008-D-0055, 11 February 2008, Guidance for Industry: Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products.

Via electronic submission:
http://www.regulations.gov/fdmspublic/component/main?main=DocketDetail&d=FDA-2008-D-0055

Dear FDA Dockets Manager:

AABB is an international association dedicated to advancing transfusion and cellular therapies worldwide. Our members include more than 1,800 hospital and community blood centers and transfusion and transplantation services as well as approximately 8,000 individuals involved in activities related to transfusion, cellular therapies and transplantation medicine. For over 50 years, AABB has established voluntary standards for, and accredited institutions involved in, these activities. AABB is focused on improving health through the advancement of science and the practice of transfusion medicine and related biological therapies, developing and delivering programs and services to optimize patient and donor care and safety.

AABB appreciates this opportunity to comment on this draft guidance document. On behalf of the AABB Cellular Therapies Committee, the following comments to the draft "*Guidance for Industry: Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products*" are submitted.

The comments are arranged in the following format:
Section – language from draft guidance reprinted with page # and other identifying information.
Recommendation/Clarification – recommendation with rationale or point requiring clarification.

General Comment – AABB understands that current regulations require the use of a "standard" method for microbiological detection unless an alternative method can be shown to be equivalent. We are pleased that FDA recognizes that there have been many advances in the methodology for detection of bacterial contamination. There is certainly a body of published evidence that demonstrates the superiority of automated methods to thioglycollate and broth

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cultures, which are generally less sensitive and specific as well as fraught with numerous complicating issues.

Section – III. GENERAL CONSIDERATIONS FOR VALIDATION OF AN RMM FOR CELL-BASED PRODUCTS, C. What Elements Should Be Considered to Validate an RMM? (page 5) **– "…***We recommend that validation include comparison studies between the RMM and the method described in 21 CFR 610.12 to demonstrate equivalence as required under 21 CFR 610.9. For this purpose, equivalence may be demonstrated by evidence that the performance of the RMM assay provides assurances equal to or greater than assurances provided by the method in 21 CFR 610.12. Because validation studies of microbiological methods encompass a large degree of variability, the concept of the RMM being "equal to" or "greater than" the traditional method is demonstrated in parallel comparisons to the traditional method using as many identical parameters as possible to claim equivalence..."*

Recommendation – There have been extensive validation studies published of commercially available rapid microbial methods (RMM) with a variety of cellular products. These studies involved parallel testing with the method described in 21 CFR 610.12. We contend that an establishment that adopts one of these methods should be permitted to perform an abbreviated study, if the following assumptions are met:

- Adequate data are available from the published studies.
- Ancillary materials used in production are comparable to those used in the published studies.
- Sample volume is comparable to that used in the published studies.
- Initial Installation Qualification, Operational Qualification and Performance Qualification of the automated system were performed by the manufacturer and laboratory.

The abbreviated study should only be required to demonstrate the following:

- The specific product(s) manufactured by the facility is/are not bacteriostatic or fungistatic in the RMM system.
- Environmental isolates specific to the product and facility can be detected.

Therefore, in such a situation, we recommend that FDA consider permitting the performance of an abbreviated study not requiring parallel testing with the standard method and using products and environmental isolates specific to the facility, in addition to a small number of organisms representing a variety of growth characteristics. Such a study would be much less burdensome and decidedly less expensive, especially for the smaller establishments and academic laboratories that do not have the resources or expertise to perform these studies in-house.

Section – III. GENERAL CONSIDERATIONS FOR VALIDATION OF AN RMM FOR CELL-BASED PRODUCTS, E. How Do I Design the Method Comparison Studies? (page 9) – *"...Prepare dilutions of challenge organisms such that final concentrations of solutions contain between 10-99 CFU/sample for currently approved sterility methods. Ensure that CFU determination accurately reflects the actual number of CFUs mixed with the sample(s), such as by plating respective dilutions of the inoculation..."*

Clarification – The inclusion of a recommended final concentration of 10-99 CFU per sample of challenge organisms for the currently approved method is appreciated and valuable for determining comparability. In that regard, it is our interpretation that the detection of 10-99 CFU in a product sample tested using a RMM would indicate sensitivity equivalent to that of the currently approved method. We believe the final document would benefit from clarification of this point.

Questions concerning these comments may be directed to Joseph L. Giglio, Deputy Director, Regulatory Affairs, AABB jgiglio@aabb.org

Sincerely,

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Chair, AABB Cellular Therapies Committee