Aventis Pasteur

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04 November 2003

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

Re: Docket No. 2003D-0382; Draft Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice [68 Federal Register 52782, September 5, 2003]

Dear Sir/Madam,

Aventis Pasteur Inc. of Swiftwater, Pennsylvania thanks the Food and Drug Administration (FDA) for the opportunity to further comment on the above-referenced draft guidance for industry entitled, "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice." Aventis Pasteur Inc. is part of the Aventis Pasteur family of companies, which consists of the parent firm Aventis Pasteur SA, headquartered in Lyon, France, Aventis Pasteur Inc., and other subsidiaries (collectively Aventis Pasteur). In turn, Aventis Pasteur SA is a subsidiary of Aventis SA.

Aventis Pasteur is a world leader in vaccines and produces more than one billion doses of vaccines every year to immunize 400 million people around the world. Aventis Pasteur, in close consultation with the US public health establishment, including the FDA, and Centers for Disease Control and Prevention (CDC), strives to alleviate the suffering and death of vaccine-preventable diseases.

We offer the following comments for your consideration concerning the FDA's solicitation of responses as they apply to the Biologics (Vaccine) industry.

Validation of Aseptic Processing and Sterilization (Begins Line 690, Page 21 PDF Document)

Duration of an APS

Aventis Pasteur believes there should be a balance between the number of vials, length of time, and aseptic operations/operator interventions in setting up simulations. We do not concur with the FDA proposal of having to routinely perform an APS for maximum periods of time as proposed in the draft Guidance. We believe it is appropriate to include this as part of the initial validation of a line; however, we do not support the position that it should be routinely repeated, unless there is a change or incident that requires a re-evaluation of the maximum time.

2003D-0382 C28

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Validation of Aseptic Processing and Sterilization (Begins Line 921, Page 26 PDF Document) (A), 9

"In the case of a media fill failure, a comprehensive investigation should be conducted, surveying all possible causes of the contamination. The effects on commercial drugs produced on the line since the last successful media fill should also be assessed."

Aventis Pasteur would prefer to see this section expanded to provide a clearer understanding of what measures FDA believes are appropriate in place of the word "assessed." For example, is the concern the same throughout the entire interval, or what are the indicators for raising the level of concern? Is FDA advocating quarantine of products until a media fill is determined to be successful? What does FDA recommend as the considerations that should go into disposition decisions for implicated batches?

Laboratory Controls (Begins Line 136, Page 32 PDF Document)

Environmental Monitoring

It is Aventis Pasteur's belief that the Environmental Monitoring section of the Draft Guidance requires some more definition in regard to the frequency of requirements for air monitoring. There is a somewhat vague statement that in the Environmental Monitoring Program monitoring includes the entire process and all shifts, but there is no recommendation as to the frequency of specific types of Environmental Monitoring. This point is particularly true for air monitoring (particle monitoring, air active and passive monitoring).

Is it FDA's position that settling plates are required? In Table 1 Air Classifications (Line 143, Page 5) there is mention that settling plates are indeed optional.

Aventis Pasteur also recommends that the document be elaborated, specifically in regard to information and recommendations on validation of a facility. There is some mention of site determination, but no additional specifics. It would potentially be of benefit for FDA to reference the ISO criteria since the 209E guidelines have been inactivated.

Appendix 3: Processing Prior to Filling and Sealing Operations (Begins Line 809, Page 53 PDF Document)

Aseptic Connections

"Procedures (e.g., aseptic connections) that expose a product or product contact surfaces should be performed under unidirectional airflow in a Class 100 (ISO 5) environment."

Aventis Pasteur believes that this requirement is no longer applicable where there is an alternative that can be validated. Aventis Pasteur has developed, and presented to FDA, a validated means of making aseptic connections without the need for Class 100 cover. We believe that this Guidance should include a statement such that, *"..As an alternative to manual procedures for making aseptic connections, a Sterile*

Connecting Device can be used for aseptic connections in unclassified zones as long as the process is validated." Aventis Pasteur believes this is an important point as advances in technology are always improving the levels of sterility assurance.

Appendix 3: Processing Prior to Filling and Sealing Operations (Begins Line 809, Page 53 PDF Document)

Aseptic Monitoring from early manufacturing steps

The draft Guidance states: *"Microbiological and airborne particulate monitoring should be performed during operations." "Personnel monitoring should be performed in association with operations."*

It is Aventis Pasteur's belief that most companies involved in aseptic manufacturing processes perform glove touch tests daily on every employee, but do not perform gown tests. We believe that the reference to personnel monitoring should be modified to state that "...daily glove touch tests should be applied" to better define this and to avoid any confusion around the terming of "personnel monitoring."

On behalf of Aventis Pasteur Inc., we appreciate the opportunity to comment on this draft guidance and thank you for your consideration of these responses. Should you wish to discuss any of our comments or concerns further, please address inquiries directly to Kenneth P. Guito, Global Head, Regulatory Policy and Intelligence, by telephone at (570) 839-4212, or by email at ken.guito@aventis.com.

Sincerely,

for Luc Kuykens, MD, MPH, DTM
Vice President, Regulatory Affairs, North America
and Authorized Official

LK/KPG/kh