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PDA Global Headquarters

Bethesda Towers
4350 East West Highway
Suite 150
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-0296

www.pda.org

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June 27, 2011

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

**RE: Periodic Review of Existing Regulations; Retrospective Review
under E.O. 13563; Docket Number FDA-2011-N-0259**

Dear Sir/Madam:

PDA is pleased to offer comments on the Periodic Review of Existing Regulations; Retrospective Review under E.O. 13563. PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments were prepared by a committee of experts with experience in CMC and GMP regulations, including members representing our Biotechnology and Regulatory Affairs and Quality Advisory Boards. PDA appreciates the opportunity to offer comments and wishes to thank FDA for the opportunity to do so.

PDA would like to identify the following regulations for consideration under this Periodic Review, since we believe them to be outdated and/or burdensome:

- **21CFR 610.12 regulations regarding sterility testing for biologics. We believe these regulations should be modified to apply only a subset of biologic bulk material.**
- **21CFR 211.94(c); GMP Regulations for Finished Pharmaceuticals covering drug product containers and closures**

Background of the issue:

- **21CFR 610.12 covers specific requirements for sterility testing for biologics**
- **21CFR 610.12 requires the bulk material to be tested separately from final container material**
- **21CFR 610.12 details the methodology for performing sterility testing for bulk and final container material**
- **21CFR 610.12 was drafted decades ago for older biologic production processes. Current biotechnology product production processes include advances in production controls which were not available at the time this regulation was promulgated.**

Burdensome aspects:

- Many of the current biologics (i.e., biotech products) do not have a “sterile bulk stage” and are rendered sterile upon final filtration with one or more 0.2 micron filter(s). These biologics are processed in a manner intended to provide “low bioburden” and “bioburden” limits are put in place prior to the final sterilizing filtration to assure sterile filtration into final container is within validated limits. Requiring a sterility test on bulk material where the bulk is not sterile provides no additional sterility assurance of the final drug product.
- Biologics that can be filtered through a sterilizing filter after formulation are held in storage vessels under controlled conditions to prevent microbial contamination during the step prior to final filtration. In such cases the additional bulk sterility sample must be obtained after the sterilizing filter in order to meet the requirements outlined for a bulk sterility test. In this case the sample is difficult to obtain and taking a sample after the sterilizing filter could compromise the integrity of the system given the complexity to obtain a sterile sample at this stage, thus increasing the risk of non-sterility.
- In fact, if the sterile filtered bulk is directly going to the filling line without having a receiving vessel, a sample representing the entire sterile filtered bulk, cannot be taken at all.
- The sterility test methodology outlined in 21CFR 610.12 is prescriptive and does not foster the adoption of new sterile method technologies or alignment with pharmacopeia requirements over time.

Proposal:

- Based on the fact that many current biologics are not considered to have a “sterile bulk stage”, performing a sterility test on the bulk material is of no value in this case and because of the complexity of obtaining a sterile bulk sample after sterilizing filtration may actually contribute to potential contamination of the product, PDA proposes this regulation be modified to require bulk sterility testing for those bulk materials that cannot be filtered through one or more sterilizing filters prior to filling.
 - PDA also would propose that the specific sterility method outlined in 21CFR 610.12 be removed and that reference to appropriate compendia sterility tests or other scientifically supportable test methods as outlined in the license application.
- 21CFR 211.94(c); GMP Regulations for Finished Pharmaceuticals covering drug product containers and closures

Background of the issue:

- 21CFR 211.94(c) requires that “drug product containers and closures shall be...processed to remove pyrogenic properties.”
- 21 CFR 211.94(c) further requires that such depyrogenation processes be validated.
- When originally published in draft form, PDA commented on this requirement on February 15, 2008, noting that certain containers and closures are non-pyrogenic by nature and/or design of their manufacturing processes or have been qualified not to require active depyrogenation, and recommending that validation only be required when containers and closures are actively rendered non-pyrogenic by a designated depyrogenation process.

Burdensome aspects:

- Developing, reviewing and approving validation protocols, conducting validation studies, and reviewing and approving the results of these studies for containers and closures which are inherently non-pyrogenic due to their nature and/or design of their manufacturing processes is a non-value adding work which increases costs without significantly reducing risk to the patient.

Proposal:

- We request FDA to reconsider the proposal we made in our February 15, 2008 letter; i.e.; reword 211.94(c) as follows:
 - “Drug product containers and closures shall be clean and, where indicated by the nature of the drug and its manufacturing process, sterile and non-pyrogenic to assure they are suitable for their intended use. When containers and closures are rendered actively non-pyrogenic by a designated depyrogenation process, the depyrogenation process shall be validated.”

We would be pleased to offer our expertise in a meeting with FDA to provide clarification of our comments. Should you wish to pursue that opportunity, or if there are any other questions, please do not hesitate to contact me.

Sincerely,



Richard Johnson
President, PDA

CC: Robert L. Dana, PDA
Rich V. Levy, PhD, PDA