November 3, 2003

GlaxoSmithKline

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Management Dockets, N/A
Dockets Management Branch
Food and Drug Administration
HFA-305
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Re: Docket Number 2003D-0382
Draft Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing

Dear Sir or Madam:

Enclosed please find comments from GlaxoSmithKline, both general and specific (but only those regarded as critical), for the Draft Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing. These comments are presented for consideration by the FDA. The general comments are presented first, with the critical/specific comments presented in order by section in the draft guidance.

GSK acknowledges the significant improvement that has been made to this document since the publication of the "Concept Paper" and commend FDA for the response to individual, PDA, and PQRI input. Given this progress made from the original concept paper to the current draft guidance, it would be advisable for the FDA to engage in another revision/draft, utilizing the good offices of the PQRI to resolve the outstanding issues.

GlaxoSmithKline appreciates the opportunity to provide feedback and suggestions for this draft guidance. I am submitting this guidance both electronically, (Dockets Management, Electronic Comment Submission Form) and by hardcopy. Therefore, you will receive a paper copy of this letter with two copies of the comments through the USPS.

If you have any questions about these provided comments, please do not hesitate to contact me at (919) 483-5857. Thank you for your consideration.

Sincerely,

Mary Faye S. Whisler

Mary Faye S. Whisler, Ph.D.
Assistant Director
New Submissions, North America

2003D-0382 C19

Review of Draft Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing

General Comments:

Both the industry and FDA urgently need new guidance. The guidance should enable firms to know what to expect during FDA inspections of their aseptic processing areas and it should help ensure that FDA 483 observations are based on current guidance that is based in appropriate technology, science, and best practices. This document still relies on significant interpretation by both industry and regulators. There is significant variation in the level of detail included from section to section. In addition, some of the items in this guidance are covered in other guidance documents, and we would suggest that these items (e.g. Sterility Test Requirements) be removed from this guidance document.

Specific Comments:

Section IV. Buildings and Facilities

Lines 132-136:
Cleanrooms cannot be classified under operational conditions. Classification methodology (ISO 14644) requires testing to be conducted on a predefined grid of locations within the room with it in the static mode. Cleanrooms can only be monitored in operation conditions.
RECOMMENDED TEXT: "...static conditions, room particle performance data should be derived from monitoring carried out under dynamic conditions (i.e., with personnel present, equipment in place, and operations ongoing)."

Lines 172-178 (Section A. Critical Area – Class 100 (ISO 5)
The term "work site" is too vague. Also confusion has been introduced in the sampling volume of the sampling volume and acceptance criteria. It is still assumed but not stated that ft^3 samples should be taken.

Lines 326-335 (Section D. 2. High Efficiency Particulate Air (HEPA))
Too much emphasis is placed on air velocity through HEPA filters. Unidirectional airflow sufficient to provide protection from contamination at critical locations is the main concern. Also the text suggests a frequency of testing which is higher than the industry norm of twice yearly. This type of testing is intrusive and brings its own risks to the process. The requirement for testing at a distance of 6 inches from the filter face is too prescriptive because this

distance will vary dependant on a number of circumstances and should be left to the testing agency to determine the appropriate distance.
RECOMMENDED TEXT: "HEPA filter leak testing alone is not sufficient to monitor filter performance and should be carried out in conjunction with air velocity measurement for all ISO Class 5 zones at least twice yearly."

Lines 403-405 (Section E. Design)
While it is assumed that the restriction of drains is from the ISO Class 5 (grade A grade B environments), the use of "classified" and "aseptic processing facility" could suggest that drains must be absent from formulation and service areas adjacent to the aseptic core, as these are classified areas.
RECOMMENDED TEXT: "With rare exceptions, drains are not considered appropriate for ISO Class 5 areas where aseptic filling and closure activities are conducted.

Section VI. Components and Containers/Closures

Lines 551-553 (Section A. Components)
This instruction should not be included in a cGMP guideline. This is a regulatory application issue.
RECOMMENDED TEXT: Remove the sentence, "If a component is not adversely affected by heat, and is soluble, it can be made into a solution and subjected to steam sterilization, typically in an autoclave or a fixed pressurized sterilize-in-place (SIP) vessel."

Lines 564-567 (Section A. Components)
Few components (actives and excipients) used in parenteral products are derived from sources liable to be endotoxic, such as materials of natural origin, i.e., starches and sugars, but are chemically synthesized and therefore are of low natural bio/endotoxin burden.
RECOMMENDED TEXT: "Parenteral products are intended to be nonpyrogenic. There should be written procedures for the evaluation of components (active ingredients and excipients) for their potential to be contaminated with bacterial endotoxin. Where potential contamination exists, each received lot of material should be tested to appropriate specifications (for acceptance or rejection). Any components failing to meet defined endotoxin limits should be rejected."

Lines 623-624 (Section B. 1. Preparation)
This text suggests that validation reports and protocols will be reviewed and formally approved by the finished dosage form manufacturer. This is neither desirable nor practical as contract firms may supply firms with product. It would be unrealistic to expect each firm to review and approve all validation documents.

The validation status of a contract facility will be assessed as for other cGMP activities by audit. Nor formal validation review is required.
RECOMMENDED TEXT: Remove the sentence, "The finished dosage form manufacturer is responsible for the review and approval of the contractors's validation protocol and final validation report."

Section VII. Endotoxin Control

Lines 663-664
This sentence would suggest that endotoxin challenge and removal should be introduced as an element of cleaning validation for all product contact surfaces. This is not required, as an endotoxin control program should be in place to prevent establishment of endotoxins.
RECOMMENDED TEXT: "Where the probability for endotoxin deposition exists on product contact surfaces, it can be inactivated by high temperature dry heat or removed from equipment surfaces by validated cleaning procedures."

Section IX. Validation of Aseptic Processing and Sterilization

Lines 1117-1118 (Section C. 2. Equipment Controls and Instrument Calibration)
The D-value analysis may be accepted via certification as described in USP 26, <55>, <1035>, and <1208>.
RECOMMENDED TEXT: Delete the requirement for D-value determination, so that sentence becomes "The microbial count of a biological indicator should be confirmed before a validation study."

Section X. Laboratory Controls

Lines 1297-1298 (Section B. Microbiological Media and Identification)
Classical microbiological identification techniques are sufficient in most cases. Rapid genotypic methods are only required in exceptional circumstances.
RECOMMENDED TEXT: "Rapid genotypic methods are recommended for purposed of identification in exceptional cases where it is critical to match micro-organisms, as these methods have been shown to be more accurate and precise than biochemical and phenotypic techniques."

Section XI. Sterility Testing

Lines 1425-1426 (Section E. 1. Identification (speciation) of the organism in the sterility test)
As stated in the comment for lines 1297-1298 (above), classical identification techniques are sufficient in most cases. The use of nucleic acid-based methods should only be considered in exceptional circumstances.
RECOMMENDED TEXT: Delete the sentence, "Nucleic acid-based methods are recommended for microbial identification purposes."

Appendix 1. Aseptic Processing Isolators

Lines 1683-1684 (Section D. 3. Frequency)
This statement is too prescriptive because not all breaches in integrity present a risk to the product, for example, a minor leak in the isolator external case while under continuous positive pressure.
RECOMMENDED TEXT: "Breaches of integrity should be investigated. If the investigation leads to the conclusion that the environment has been compromised, than any product that may have been impacted by the breach should be rejected."

Appendix 3. Processing Prior to Filling and Sealing Operations

Lines 1853-1854 (Section A. Aseptic processing from early manufacturing steps)
The validation of the integrity of the bulk containers is required, but not as a part of the media fill exercise.
RECOMMENDED TEXT: "The transport of bulk tanks or other containers should be validated."

Lines 1855-1856 (Section A. Aseptic processing from early manufacturing steps)
The validation for the integrity and transportation of bulk holding tanks only requires a repeat when a change to the process is made. There is no requirement for ongoing performance testing for aseptic filling.
RECOMMENDED TEXT: Delete the sentence, "Process simulation studies for the formulation stage should be performed at least twice per year."

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