Vectech

Memorandum

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DATE: November 4, 2003

TO: Dockets Management Branch (HFA – 305)

FROM: Vectech Pharmaceutical Consultants, Inc.

RE: Docket No. 03D - 0382

MESSAGE:

Introduction

The following comments regarding the **Draft Guidance for Industry Sterile Products Produced by Aseptic Processing – Current Good Manufacturing Practice** were gleaned from industry participants of two separate seminars. The intent of each seminar was the same; each was designed to foster discussion and generate feedback about this draft guidance. This response is divided into six different sections

- General Concerns
- Environmental Monitoring Concerns
- Building and Facilities Concerns
- Validation of Aseptic Processing and Sterilization Concerns
- Endotoxin Control Concerns
- Components and Container Closure Concerns.

The order in which the sections appear is not intended to represent priority, each of these concerns carries equal merit.

General Concerns

The first concern is the use of "Current Good Manufacturing Practice" in the title of the document. GMP's have always appeared in the Code of Federal Regulations and are law, the use of this term in an FDA guidance document, which contains "nonbinding recommendations", will create ambiguity among the industry as to what is in fact GMP. GMP's should not have any ambiguity surrounding them.

Some among our group have expressed concern that there is no clear wording about the regulatory status of items not covered in this guidance. For example, ampoules are not covered in this guidance. While we understand that the FDA cannot provide guidance on every facet of aseptic processing, there should be wording in the guidance about the extent to which it may be applied. This concern is made more significant when one considers the fact that the FDA will be using this document to train investigators. Manufacturers and inspectors alike should understand when this guidance applies and when it does not.

In line 1440 the term "sterility test positive trends" is used in providing guidance as to when to review operations. A definition of "trends" in this context would be very helpful to this decision making process since an insufficient number of data points are present to generate statistical trends.

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We recommend a line be added to the guidance on interventions during processing. The guidance document addresses some of the documentation practices for recording interventions in the batch record. Manufacturers would like to see inclusion of the data used to support the intervention recorded in the batch record.

Environmental Monitoring

In the section on 'Establishing Levels and a Trending Program' line 1208 calls for a written procedure to establish identification actions to be taken. We recommend this guidance be changed to reflect the need to do routine identification of potential isolates, but not to call for identification of potential isolates each time an area is tested. Identifications are very time consuming and costly to do. This requirement is especially restrictive when counts are within acceptable limits.

Surface testing is given to a high propensity of false positives, as a result this data is often meaningless. We would like to see the surface testing called for in line 1247 changed. Surface testing should be part of investigations, but not as a routine part of GMP's.

In line 1297 the draft guidance calls for rapid genotyping methods to be implemented for purposes of identification. We would like to see this changed to include other methods, as rapid methods could be cost prohibitive for smaller manufacturers and others that may not have the capital to implement such costly measures.

Building and Facilities

We recommend that the guidance call for air classifications to be stipulated by the requirements of the country in which the product is intended to be distributed.

The requirements for air changes called for in line 248 is an arbitrary number. We would like to see the guidance call for a "sufficient number" of air changes per hour to maintain the particulate requirements for the specific classification of each room. The problem with an arbitrary number of air changes is the potential for creating unnecessary vortices in a critical area. If a piece of equipment presents a challenge for controlling the vortices created by maintaining 20 air changes per hour, the manufacturer should be able to reduce the amount of air flow to a point where the classification is maintained and vortices are reduced or eliminated.

Validation of Aseptic Processing and Sterilization

This section calls for autoclave requalification to be conducted on a schedule based on "the age of the sterilizer" (line 1073). We would rather see the schedule for requalification be based on adequate procedures, maintenance, trending, and history all of which are more important to assessing the capability of an autoclave than simply the age of the equipment.

Endotoxin Control

Although there is no specific mention of endotoxin control for API's, we are concerned about endotoxin control being required for bulk pharmaceutical manufacturers.

A 3-log reduction of endotoxin levels, stated in line 669, for all components is needlessly over restrictive. We would like the guidance document to take into account the use of each component, this way the endotoxin levels could be based on the nature and intended use of each component.

There is great concern among our group about the wording that appears in line 650 regarding the use of products in higher risk populations. Manufacturers cannot reasonably be held accountable for improper use of their products. The decision to use certain products on patients in higher risk populations should fall to physicians that have an understanding of that patient's medical history, medical needs and who is properly trained to make exactly this kind of decision. Industry can place indications, contraindications and warnings on labeling but cannot be responsible for the ultimate use, or misuse, of their products.

Components and Container Closures

The wording in line 624 that calls for finished dosage form manufacturers to be responsible for the "review and approval" of contractor's validation protocol and final validation report should be changed to exclude the word approval. We feel it necessary to review contractor's validation protocols and reports but the approval suggestion places an undue burden on both the final manufacturer and the contractors.

We would like to see the wording in line 629 about the penetration of air into containers changed to include an acceptable, quantifiable leak rate. Of course, the sterile product would still have to meet the requirements for sterility, but some container closure systems may permit leakage without causing a contamination problem. Bulk pharmaceutical storage is a good example of just this kind of closure system.

Questions and Comments

Questions and comments about this response should be directed to the following address:

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