ALLERGAN

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October 28, 2003

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

Dear Sir:

Re: GUIDANCE FOR INDUSTRY - Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice
CDS029\REGAFF\guidanc\1874dft.doc

These comments are intended to improve the new Aseptic Processing Guideline Draft by clarifying certain sections of the document. Each comment will include the line number from the guidance document.

Line 143 – TABLE 1 – Air Classifications

Microbial Levels – The Microbial Action Level values listed for the different Clean Area Classifications are not statistically different from each other. Microbial count levels are usually given with a ± 0.5 $\log_{10}$ error. Therefore, numbers in the settle plate column are statistically the same for the first three air classifications. Similarly, active air monitoring levels for the same classifications are not significantly different. Alert and Action Levels should be determined by scientific validation, risk evaluation, and trending of environmental data.

Listing particle levels per ft^3 (American Classification) and particle levels per m^3 (ISO Classification) in the same table implies that counts may be performed using either method, whereas microbial counts must be taken per m^3 or indirectly by settle plate. By listing both classification systems, it is not clear which system is preferred by the agency. Throughout the guidance document, the air classifications are mentioned in tandem with the American Classification first and the ISO in parenthesis. This representation leads to confusion about the appropriate classification system to use.

The guidance lists microbial levels for Clean (Controlled) Area Air and lists no microbial levels for work surfaces, walls, etc. and personnel, gloves, and garb. This approach is inconsistent. A better tactic would be to permit each facility to determine all microbial levels by scientific validation and risk assessment of all areas.

There is no instruction presented for collecting the sampling volume required to meet the criteria presented in the table. This can lead to different approaches for sampling for example 1) the sampling is performed discontinuously throughout the filling or compounding in one ft^3 samples and reported in particles per ft^3 or 2) the total sample volume (from example 1) summed to one volume and converted into m^3, or 3) the volume or sampling of the air required must be collected continuously until at least the m^3 volume is collected and data recorded. Are all methods acceptable?

Line 214

The word "*normally*" is very subjective. Is there a definition that is acceptable for normally? For example, samples from Class 100 (ISO 5) environments should *normally* yield no microbiological contaminants. Is one time in five or ten normal? The term appears in other sections of the guidance document.

Line 238

Measurement of air pressure differential units has changed to Pascals, but Pascals is not consistently used throughout the guidance draft (e.g. Line 1596).

Line 407

While in general agreement with the requirements for sterilization of the equipment used in the aseptic filling process, it should be noted that for some items such as large hoppers and belts, sanitization in place prior to each fill will reduce the possibility of microbial contamination. Sterilization of each of these items followed by an extra aseptic assembly step is a higher microbial risk than a validated sanitization in place procedure.

Line 841

For the Media Fill growth promotion procedure, there is no clear guidance as to when the samples (containers) should be removed for testing. 1) One method is the removal of samples for a growth promotion test randomly during the Media Fill (prior to incubation, but not after interventions) or 2) a second is the performance of the growth promotion test after the incubation and observation of the Media Fill containers. 3) Using both the previous examples to collect samples and to perform the growth promotion is another possible procedure. There have been conflicting observations from field inspectors as to the correct method. Some inspectors require the first method while others only the second and another group requires both methods.

Line 915

If the video tape of a Media Fill has been examined and all events documented, does the tape have to be retained indefinitely? We would recommend allowing the tape to be discarded after a specified period of time defined in a standard operating procedure.

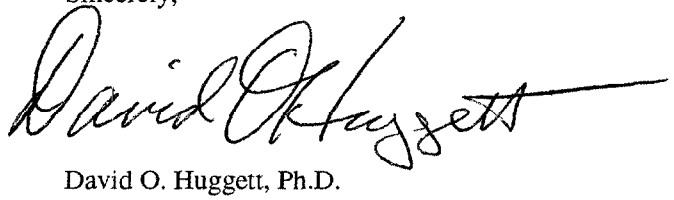
Line 942

Blow-Fill-Seal aseptic filling lines may be in use for extended periods of time (over many days) and fill over 1,500,000 containers. It is unreasonable to limit the number of contaminated units to a maximum of two (2) for this type of filling. One alternative may be limiting contamination to an average of one (1) contaminated unit per day (24 hours). A Media Fill may often exceed 60,000 containers.

Line 1825

There is a typographical error that the word "sterilized" is incorrectly spelled.

Sincerely,



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