November 3, 2003

Via fax and UPS

Dockets Management Branch (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Draft Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice [Federal Register Volume 68, No. 172, page 52782, September 5, 2003]

Dear Sir/Madam:

Aventis appreciates the opportunity to comment on the above-referenced draft guidance entitled "*Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*".

The Agency states that this guidance is intended to help manufacturers meet the requirements in the Agency's current good manufacturing practice regulations when manufacturing sterile drug and biological products using aseptic processing.

We offer the following comments and questions for your consideration.

GENERAL COMMENTS:

Harmonization:
There are some aspects of this draft guidance document that appear to improve global harmonization, for example, approach to aseptic processing vs Terminal Sterilization and approach to environmental monitoring at rest & in operation (dynamic condition). However, there are some new additions that do not occur in other regulatory approaches, for example, the introduction of the concept of having a class 1000 area.

This guidance document does not harmonize with either EU Annex 1 or ISO 14644 series. The guidance does not allow averaging of microbiological results, and requires dynamic air classification.

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21 CFR Regulation Citations:
Throughout the draft guidance document, 21 CFR Part 210 and 211 regulations are cited. We suggest that guidance be provided to support each regulation cited.

SPECIFIC COMMENTS:

Lines: 114-115: "In such cases, a manufacturer can explore the option of adding adjunct processing steps to increase the level of sterility confidence."

Recommendation: For clarity, we suggest adding text to define *"adjunct processing steps"* and *"sterility confidence"*.

Lines 142 – 144: *(Table 1)- Air Classifications*

Recommendation: Since the table covers more than just air classification requirements (i.e., microbial levels) and pertains solely to aseptic processing areas, we suggest revising the title of the table to "Air Monitoring for Aseptic Processing".

We also suggest that values should be presented in the table header (column 1) as the maximum number of particles.

Line 146: *Footnote (a) – "All classifications based on data measured in the vicinity of exposed materials/articles during periods of activity."*

Recommendation: We suggest revising Footnote (a) to read as follows: *"Initial clean room classification should include an assessment of air quality under static conditions. The room should operate within the expected limits during periods of activity."*

Lines 147-148: *Footnote (b) – "ISO 1644-1 designations provide platform particle concentration values for clean rooms in multiple industries, An ISO 5 particle concentration is equal to Class 100 and approximately equals EU Grade A."*

Recommendation: Class 100 (as defined in FS209E) and ISO Class 5 (as defined in 14644-1) both have requirements for particles of other sizes that are not quite equivalent. For example, Class 100 allows 26500 x 0.2µm and 10600 x 0.3 µm particles per m^3, whereas ISO 5 only allows 23700 and 10200 respectively. ISO 5 also has requirements for 1 µm and 5 µm particles, which Class 100 does not. If there are requirements for these particle sizes, we suggest that the guidance provide clarification.

We also suggest that there should be international harmonization in microbiological action levels. The proposed microbiological limits are stricter than both the current USP and the EU guide Annex. The EU guide permits averaging, which is not mentioned in the FDA guidance and so presumably not permitted.

Line 152: *Footnote (e) – "Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants."*

Recommendation: It is unclear why Table 1 includes the value of "1" if Class 100 (ISO 5) environments should normally yield no microbiological contaminants. Footnote (e) adds confusion as to whether the action level is 1 or zero. Therefore, we suggest that this footnote either be deleted or replaced with the following text: *"The count should be < 1, as verified by averaging."*

Lines 198-200: *"The velocity parameters established for each processing line should be justified and appropriate to maintain unidirectional airflow and air quality under dynamic conditions within a defined space (Ref.3).[4]"*

and

Footnote 4: "A velocity from 0.45 to 0.51 meters/second (90 to 100 feet per minute) is generally established, with a range of plus or minus 20 percent around the set point. Higher velocities may be appropriate in operations generating high levels of particulates."

Recommendation:

- For clarity, we suggest adding text to define *"defined space"*.
- With regard to Footnote 4, it is suggested that it is clearly stated that this is a guidance value, which then would be harmonized with the EU GMPs, Annex 1.
- Where it is scientifically and technically justified & validated, we suggest that the option should be open to use any alternative velocity that is effective, not simply a "higher" one. Depending on the exact facilities & process, it may prove better to use a lower, controlled, velocity. Where this is validated, the approach should not be unnecessarily proscribed. For example, if smoke studies at lower velocities show better laminarity, then it should be acceptable to operate in this defined range.

Lines 229 - 230: *"Depending on the operation, manufacturers can also classify this area as Class 1,000 (ISO 6) or maintain the entire aseptic filling room at Class 100 (ISO 5)."*

Recommendation: We suggest that the additional category ISO 6 (Class 1000) in the context of Pharmaceutical manufacturing should be deleted for the following reasons:

- There is no real technical need for this class.
- The category does not exist in any other pharmaceutical references.
- It is impractical.
- Strides should be made toward international harmonization whereas the introduction of a new class tends to move against this.
- The microbiological criteria for this category are new and are not consistent with any other existing document on this topic, including the USP.
- The proposed new category would generate uncertainty as to what criteria would be expected, depending on the process (ref. Line 229 "depending on the operation")

Lines 238-241: *"For example, a positive pressure differential of at least 12.5 Pascals (Pa)[5] should be maintained at the interface between classified and unclassified areas. This same overpressure should be maintained between the aseptic processing room and adjacent rooms (with doors closed)."*

Recommendation: The draft guidance indicates that differentials of 12.5 Pascals need to be maintained with respect to all rooms adjacent to an aseptic processing room. If this includes rooms of the same classification, then this is in excess of existing GMP requirements, which require this differential only between rooms of different classification.

Due to the cumulative differential pressure steps, this may result in very high pressure (relative to ambient) at the central core. It may also cause problems with balancing the overall cascades of airflow / pressure differentials (e.g., where a hot air sterilizer tunnel is installed there would be a very high differential between outlet and inlet to the tunnel).

Lines 247-250: *"For Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve at least 20 air changes per hour would be typically acceptable. For areas of higher air cleanliness, significantly higher air change rates will provide an increased level of air purification."*

Recommendation: This requirement for air changes substantially higher than 20 per hour is normally unnecessary and may be difficult to achieve depending on the size & design of the area.

Lines 264-266: *"Compressed gases such as air, nitrogen, and carbon dioxide are often used in cleanrooms and are frequently employed in operations involving purging or overlaying."*

Recommendation: For clarity, we suggest rephrasing this sentence to read as follows: *"Compressed gases such as air, nitrogen, and carbon dioxide are often used in cleanrooms and are frequently employed in operations involving purging and/or overlaying."*

Lines 272-273: *"Sterilized holding tanks and any contained liquids should be held under continuous overpressure to prevent microbial contamination."*

Recommendation: We suggest that emphasis should be put on confirmation of integrity rather than an absolute requirement to have overpressure in all cases. Overpressure on a holding vessel may adversely affect the filling process, for example, dosing consistency. Hence, it is often technically difficult to meet the requirement to have the holding vessels always subjected to overpressure during the filling process. Alternative techniques such as pressure/vacuum testing of the vessel/system may be appropriate. Positive pressure maintenance is a good technique, but is not currently mandated by GMPs, provided that the vessel integrity and filter integrity are controlled.

Lines 287-289 : *"Therefore, leak tests should be performed at suitable time intervals for HEPA filters in the aseptic processing facility. For example, such testing should be performed twice a year for the aseptic processing room."*

Recommendation: We suggest that the minimum frequencies for testing should be based on ISO recommendations (ISO 14644-2). More frequent testing may be done based on risk analysis and routine performance data. We also suggest that testing be performed twice per year in the critical zone (ISO 5) and once per year for HEPA filters in lower categories.

Lines 292-294: *"Among the filters that should be leak tested are those installed in dry heat depyrogenation tunnels commonly used to depyrogenate glass vials."*

Recommendation: We suggest adding text to provide clarification that leak tests on HEPA filters located in the heating zone of dry heat depyrogenation tunnels need to be conducted at the room-temperature state (as it is not possible to perform the test whilst the tunnel is hot).

Lines 297-298: *"Dioctylphthalate (DOP) and Poly-alpha-olefin (PAO) are examples of appropriate leak testing aerosols."*

Recommendation: Other leak testing agents are also appropriate. We suggest that Di-Ethyl-Hexyl-Phthalate (DEHS) be added to the list of appropriate leak testing aerosols, as this is a well-defined compound with specific characteristics. We also suggest that a reference to the international standard EN1822 be added to the guidance as it contains a list of proven and recommended aerosol materials.

Lines 310-316: *"Performing a leak test without introducing a sufficient upstream challenge of particles of known size upstream of the filter is ineffective for detecting leaks. For example, depending on the accuracy of the photometer, a DOP challenge should introduce the aerosol upstream of the filter in a concentration ranging from approximately 25-100 micrograms/liter of air at the filter's designed airflow rating. The leak test should be done in place, and the filter face scanned on the downstream side with an appropriate photometer probe, at a sampling rate of at least one cubic foot per minute."*

Recommendation: We suggest that this section be revised to allow for the use of alternatives that provide more modern and improved techniques, such as laser counters. The draft guidance currently refers only to photometers for the detection of particles. The laser counter method is a reference method in ISO/DIS 14644-3. The final guidance document should allow for developments and new techniques. The use of laser particle counters as detection instruments is now common in the Industry.

Lines 326-335: *"HEPA filter leak testing alone is not sufficient to monitor filter performance. This testing is usually done only on a semi-annual basis. It is important to conduct periodic monitoring of filter attributes such as uniformity of velocity across the*

filter (and relative to adjacent filters). Variations in velocity generally increase the possibility of contamination, as these changes (e.g., velocity reduction) can have an effect on unidirectional airflow. Airflow velocities are measured 6 inches from the filter face and at a defined distance proximal to the work surface for HEPA filters in the critical area. Regular velocity monitoring can provide useful data on the clean area in which aseptic process is performed. HEPA filters should be replaced when non-uniformity of air velocity across an area of the filter is detected or airflow patterns may be adversely affected."

Recommendation: The intervals of regular monitoring are not specified, but there is an implication that it should be performed more regularly than once every 6 months. This may be unnecessarily frequent as airflow velocity changes only occur gradually over long periods of time. We suggest that velocity tests concurrent with the filter leak testing should be adequate.

Line 348: *"...clean area are essential to achieving high assurance of sterility (Ref. 4)."*

Recommendation: Please correct minor typographical error: *"sterilty"* should read as *"sterility"*.

Lines 370-372: *"For example, lyophilization processes include transfer of aseptically filled product in partially sealed containers."*

Recommendation: For clarity, we suggest rephrasing this sentence to read as follows: *"For example, lyophilization processes include transfer of aseptically filled product in partially sealed/closed containers."*

Lines 373-375: *"Facility design should ensure that the area between a filling line and the lyophilizer and the transport and loading procedures provide Class 100 (ISO 5) protection."*

Recommendation: The current wording could be interpreted as meaning that the room itself must be classified to ISO 5 in the area between filling and the lyophilizer. We suggest revising the text so that the guidance document simply states that the protection should be according to ISO 5. There are several other methods of achieving this; for example isolator technology or laminar flow transfer carts.

Lines 403-405: *"Processing equipment and systems should be equipped with sanitary fittings and valves. With rare exceptions, drains are not considered appropriate for classified areas of the processing facility."*

Recommendation: The document states: "With rare exceptions, drains are not considered appropriate for classified areas of the aseptic processing facility." However, the glossary indicates the definition of "aseptic processing facility" as including the entire building, not only the aseptic zone.

We agree that drains should not be present in the higher categories of classified areas (e.g., aseptic processing rooms). However, correctly designed drains are necessary in some of the lower category areas, for example, locations of washers and compounding.

We suggest that the position set forth in the guidance document should be more precisely defined. We also suggest harmonizing the position with the EU GMPs, requiring that sinks and drains should be prohibited in "ISO 5" to "ISO 7" areas (classified in dynamic state). Drains should be excluded from critical and direct support locations, but are required in some of the process rooms that are not directly connected to the critical aseptic operation.

Lines 432-433: *"Supervisory personnel should routinely evaluate each operator's conformance to written procedures during actual operations."*

Recommendation: Existing procedures, including routine supervision, documented training, deviation records and internal audits are adequate to give a comprehensive control. The addition of yet more evaluation seems unnecessarily complex.

We suggest that the text in Lines 432-433 be revised to read as follows: *"There should be adequate supervision to ensure each operator's conformance to written procedures during actual operations."*

Line 442: *"Between uses, instruments should be placed only in sterilized containers."*

Recommendation: The text indicates that instruments are permitted only to be stored in sterilized containers. For clarity, we suggest adding text indicating that storage of instruments can be permitted in a protected environment where the item does not touch a non-sterilized surface. For example, instruments can be stored in an appropriate location under ISO 5 protective air.

Line 443: *"Instruments should be replaced as necessary throughout an operation."*

Recommendation: For clarity, we suggest revising the text to read as follows: *"Instruments should be replaced when any aspect of sterility is thought to be compromised so as to render the instrument non sterile, throughout the operation."*

Line 445-446: *"After initial gowning, sterile gloves should be sanitized to minimize the risk of contamination. Personnel should not directly contact sterile products, containers, closures, or critical surfaces"*

Recommendation: For clarity, we suggest revising the text to read as follows: *"After initial gowning, sterile gloves should be regularly sanitized to minimize the risk of contamination. Personnel should not directly contact sterile products, containers, closures, or critical surfaces without appropriate sterilized gloves."*

Lines 515-517: *"The quality control unit should establish a more comprehensive monitoring program for operators involved in operations, which are especially labor intensive (i.e., those requiring repeated or complex aseptic manipulations)."*

Recommendation: We suggest that this is an unnecessary division that effectively gives two classes of filling operators. This is very difficult to administer. Also, it is important that all staff in the area partaking in permitted interventions are adequately monitored. Having different monitoring procedures may be mistaken to indicate that some simpler operations are not critical, when in fact they are.

The most negative impact on the product is created by the kind of intervention performed by the operator and not by the degree of labor intensiveness. All operators who may take part in permitted interventions that could conceivably have a potential risk of product contamination must be monitored. The microbiological limits are already very tight indeed and it is unreasonable to have different classes of "criticality".

Line 600: *"Pyrogen on plastic containers can be generally removed by multiple WFI rinses."*

Recommendation: For clarity, we suggest revising Line 600 to read as follows: *"Pyrogen on plastic containers can be generally removed by adequate procedures such as multiple WFI rinses."*

Lines 618-620: *"Silicone used in the preparation of rubber stopper should meet appropriate quality control criteria and not have an adverse effect on the safety, quality, or purity of the drug product."*

Recommendation: For clarity, we suggest revising Lines 618-620 to read as follows: *"Silicone used in the preparation of rubber stoppers should meet appropriate quality control criteria and not have an adverse effect on the safety, quality, or purity of the drug product, as determined by appropriate quality control testing."*

Lines 629-630: *"A container closure system that permits penetration of air, or microorganisms, is unsuitable for a sterile product."*

Recommendation: Penetration by air occurs in many forms of packaging that is used for sterilization (e.g. sterilization packs & bags). It is the penetration of microorganisms that is the risk in these cases. Hence, we suggest that this statement is not correct in cases where the containing pack is designed to filter the air free of microbial contaminants.

Lines 660-661: *"Endotoxin control should be exercised for all product contact surfaces both prior to and after sterile filtration."*

Recommendation: We suggest that clarification be provided regarding this statement. It is unclear what is expected on this point, particularly regarding the frequency of both prior to and after sterilization. If this statement relates specifically to cleaning validation,

then perhaps it is a reasonable concept. However, if it relates to routine testing, the approach seems unreasonable.

Lines 682-687: *"The total time for product filtration should be limited to an established maximum to prevent microorganisms from penetrating the filter. Such a time limit should also prevent a significant increase in upstream bioburden and endotoxin load. Sterilizing-grade filters should generally be replaced following each manufactured lot. Because they can provide a substrate for microbial attachment, maximum use times for those filters used upstream for solution clarification or particle removal should also be established and justified."*

Recommendation: For clarity, we suggest adding the following text directly after Line 687: *"Integrity testing before and after use should also be specified in standard operating procedures that are pertinent to the use of these filters and appropriate investigations performed on any lot suspected of being compromised."*

Lines 722-724: *"Media fill studies should simulate aseptic manufacturing operations as closely as possible, incorporating a worst-case approach. The media fill program should address applicable issues such as:"*

and

Line 739: *"operator fatigue"*

Recommendation: We consider it to be generally impractical to artificially simulate fatigue, as the process should be designed to minimize fatigue.

Lines 758-760: *"All personnel who enter the aseptic processing area, including technicians and maintenance personnel, should participate in a medial fill at lease one a year."*

Recommendation: Planned interventions during media fills are logical and reasonable, however, requiring every person from maintenance who may enter the aseptic area to participate once a year may not be practical.

Lines 877-878: *"Each media-filled unit should be examined for contamination by personnel with appropriate education, training, and experience in microbiological techniques."*

Recommendation: For the inspectors (readers) of vials it is important to have regular eye examinations by an ophthalmologist. These should be mandatory for those who investigate the content of a contaminated vial.
Provided that the inspectors are well trained and have a good understanding as to what they are looking for, this aspect is more important than having detailed experience in microbiological techniques.

Any detected or suspect containers should be passed on for further detailed microbiological testing by an experienced microbiologist.

Lines 879-881: *"Clear containers with otherwise identical physical properties should be used as a substitute for amber or other opaque containers to allow visual detection of microbial growth."*

Recommendation: We suggest that other approaches should be permissible as an occasional option for use if necessary, for example, transferring to clear containers for inspection after incubation. For some particular containers it may not be feasible to source a visually clear alternative.

Lines 897-898: *"If written procedures and batch documentation are adequate, these intervention units do not need to be incubated during media fills.[9]"*

and

Footnote 9: *"To assess contamination risk during initial aseptic setup (before fill, valuable information can be obtained by incubating all such unites that may be normally removed."*

Recommendation: Data would have no value, as it is not representative of risk or exposure of the actual product. Therefore, we suggest that Footnote 9 be deleted or rephrased for clarity by adding the following text: *"To assess contamination risk during initial aseptic setup (before fill), valuable information can be obtained by incubating all such units that may be normally removed. If this approach is taken, these samples should be segregated for incubation and inspection and the results should not be included in the basic acceptance criteria for the media fill. Such results from samples that are normally removed should be interpreted separately for information".*

Lines 916-917: *"Video recording of media fill has been found to be useful in identifying personnel practices that could negatively impact the aseptic process."*

Recommendation: The phrase indicating that videotaping "has been found to be useful" may initiate an approach by investigators that will deem it mandatory.

While videotaping may be useful in some cases, there are no real grounds for making it a requirement. The same function could be covered by the manual observation and assessment by experienced QC and Production personnel.

Line 935: *"When filling fewer than 5000 units, no contaminated units should be detected."*

Recommendation: Because there is no guidance on next steps when the limit is exceeded, as there is for the other quantities, we suggest adding the following text: *"One contaminated unit is considered cause for revalidation, following an investigation."*

Lines 1009-1010: *"The specific type of filter used in commercial production should be evaluated in filter validation studies."*

Recommendation: The document uses the phrase *"the specific type of filter"* should be evaluated in the filter validation study". We suggest that text be added to clarify what "the specific type of filter" means. As stated, the phrase seems to mean the actual unit (e.g., exact cartridge/capsule). However, it is currently an accepted practice to test for retention using a representative membrane that has the same membrane construction.

Lines 1073-1075: *"The formal program providing for regular revalidation should consider the age of the sterilizer and its past performance. Change control procedures should adequately address issues such as a load configuration change or a modification of the sterilizer."*

Recommendation: We suggest that the testing schedule should be consistent, not dependent on age. If there are valid indications that the machine is unreliable or inconsistent, then it should not be in use. The effectiveness of the sterilizer should be established by validation, maintenance and routine review/assessment of cycle parameters. If there are concerns on reliability, they should be promptly addressed.

Lines 1110-1112: *"Written procedures should be established to ensure that these devices are maintained in a calibrated state. For example:"*

and

Lines 1117-1118: *"The microbial count and D-valve of a biological indicator should be confirmed before a validation study."*

Recommendation: We suggest that text be added to clarify the meaning of "confirmed" in relation to D-values. If the D-value of an bioindicator must be exactly confirmed before use this would make it necessary to have specific testing devices (BIER vessels). This is not currently a GMP requirement.

We suggest that a reasonable approach would be to verify the count and control the storage and use conditions. It should be acceptable to take the supplier's figure for the D value. An empirical kill/survival time test could be performed.

We suggest that the approach be consistent with current Industry guidelines on steam sterilization.

Lines 1152-1154: *"The monitoring program should cover all production shifts and include air, floors, walls, and equipment surfaces, including the critical surfaces that come in contact with the product, container, and closures."*

and

Lines 1170-1171: *"Critical surface sampling should be performed at the conclusion of the aseptic processing operation to avoid direct contact with sterile surfaces during processing."*

Recommendation: The purpose of environmental monitoring is to assess the conditions around the critical filling operation and adjacent support areas. The product-contact

items should have been sterilized and this verified parametrically (sterilizer charts, etc) in conjunction with validation. Sampling these surfaces would effectively be a rudimentary test for sterility, and as such much less valuable than the sterilization monitoring data.

Line 1205: *"Averaging of results can mask unacceptable localized conditions."*

Recommendation: We suggest that the current sentence be replaced with the sentence *"Averaging of results should not be used in such a way that it masks unacceptable local conditions"*. This will facilitate harmonization, since averaging of results is in principle accepted in Annex 1 of the EU GMPs.

Lines 1247-1249: *"Environmental monitoring should include testing of various surfaces for microbiological quality. For example, product contact surfaces, floors, walls, ceilings, and equipment should be tested on a regular basis."*

Recommendation: It should not be necessary to test ceilings. The environmental monitoring should concentrate on realistic risk to product.

Lines 1284-1286: *"Environmental isolates often correlate with the contaminants found in a media fill or product sterility testing failure, and the overall environmental picture provides valuable information for an investigation."*

Recommendation: The incidence of microbial recovery is low, and thus correlation back to media fills etc. is less likely. The most likely correlation is that the isolates are typically from personnel. Therefore, we suggest rephrasing the sentence to read as follows: *"Environmental isolates may correlate with the contaminants found in a media fill or product sterility testing failure, and the overall environmental picture provides valuable information for an investigation."*

Lines 1297-1298: *"Rapid genotypic methods are recommended for purposes of identification, as these methods have been shown to be more accurate and precise than biochemical and phenotypic techniques."*

and

Lines 1425-1426: *"Nucleic acid-based methods are recommended for microbial identification purposes."*

Recommendation: We consider these recommendations to be too strongly suggested, as other techniques are adequate for the purposes of identification. Most QC laboratories are currently using alternatives and very few have the capability to perform genetic testing, which can also be very expensive.

Lines 1363-1365: *"Study documentation should include evaluation of whether microbial recovery from inoculated controls and product samples is comparable throughout the incubation period."*

Recommendation: We suggest that the requirement to evaluate throughout the incubation period in order to show comparability throughout the incubation be deleted as it is in excess of compendial sterility test requirements.

Lines 1377-1379: *"A written program should be in place to regularly update training of personnel and confirm acceptable sterility testing practices."*

Recommendation: We suggest adding text regarding the meaning of the term 'regularly' in order to be clear on the requirement. Since it is already a GMP requirement to keep training up-to-date, it is not clear as to whether this is an additional requirement.

Lines 1395-1396: *"The batch processing circumstances – samples should be taken in conjunction with processing interventions or excursions."*

Recommendation: We suggest removing this sentence, as it is impossible to fulfill since firms are required to remove potentially contaminated units.

Lines 1441-1443: *"A sterility positive result can be viewed as indicative of production or laboratory problems and should be investigated globally since such problems often can extend beyond a single batch."*

Recommendation: We suggest that text be added to clarify the term 'globally', as many individuals have interpreted this term in different ways. It is unclear if 'globally' is regarded in the sense of across the whole operation at a particular site or 'globally' in the sense of across different sites worldwide.

Lines 1445-1449: *"To more accurately monitor potential contamination sources, we recommend you keep separate trends by product, container type, filling line, and personnel. Where the degree of sterility test sample manipulation is similar for a terminally sterilized product and an aseptically processed product, a higher rate of initial sterility failures for the latter should be taken as indicative of aseptic processing production problems."*

Recommendation: We suggest that since incidence is very low for failures in sterility testing, especially when using closed systems and isolators, it is not necessary to trend for each of the categories.

Lines 1456-1458: *"Where a laboratory has a good track record with respect to errors, this history can help remove the lab as a source of contamination since chances are higher that the contamination arose from production. "*

Recommendation: The conclusion based purely on good laboratory history is speculative and not very helpful. Even with a good laboratory history, mistakes can occasionally occur.

Lines 1509-1510: *"All in-process data must be included with the batch record documentation in accordance with section 211.188. "*

Recommendation: We suggest that only batch relevant data should be added to the batch record. We suggest that system relevant data may be evaluated separately and linked to batch release with no strict requirement to add them to the batch record.

Lines 1611-1615: *"The classification of the environment surrounding the isolator should be based on the design of its interfaces (e.g., transfer ports), as well as the number of transfers into and out of the isolator. A Class 100,000 (ISO 8) background can be appropriate defending on isolator design and manufacturing situations."*

Recommendation: For a closed isolator or an open isolator where mousehole environments have additional local protection and/or are validated not to entrain air, "Class 100,000 (ISO 8)" should be defined as in the "at rest" state in order to be harmonized with EU GMP grade D. We suggest adding text to incorporate definitions that are appropriate for both the EU and US. We foresee issues of interpretation between Europe and the US if there is no harmonization on this topic.

Lines 1749-1751: *"The classified environment surrounding BFS machinery should generally meet Class 10,000 (ISO 7) standards, but special design provisions (e.g., isolation technology) can justify an alternate classification."*

Recommendation: For Blow-Fill-Seal applications, the text indicates particular requirements that are potentially in excess of current expectations. The environment in which BFS machine is located is indicated as Class 10,000. If interpreted as in operation, this is similar to EU grade B (EU GMPs require grade C).
Also, there are requirements for endotoxin inactivation studies on the molding process that may be difficult to conduct.

Lines 1874-1909: *REFERENCES*

Recommendation: Since these publications are widely used in industry and provide substantially more complete information on the topics covered in this guidance, we suggest adding a reference to PDA published Technical Reports.

On behalf of Aventis, we appreciate the opportunity to comment on the *Draft Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice* and are much obliged for your consideration.

Sincerely,

Erin A. Floyd for S.C.

Steve Caffé, M.D.
Vice President, Head US Regulatory Affairs