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

Re Docket No. 2003D-0382

Draft Guidance for Industry on Sterile Drug Products Produced by Aseptic Processing

Eli Lilly and Company acknowledges the effort made by FDA in the publication for comments of the FDA's Draft Guidance for Industry on "Sterile Drug Products Produced by Aseptic Processing". We also note the substantial improvements in this document from the previously published "Concept Paper". We are pleased to offer our comments in order to further improve the draft guidance.

Both industry and FDA urgently need new guidance on this topic. The guidance should enable firms to better understand FDA expectations in the area of aseptic processing and assist in the training of FDA staff on those expectations. While the guidance has made great progress, additional work is needed. The draft guidance contains a significantly greater amount of information and detail than was presented in the concept paper. As such, giving due consideration to the comments received on the draft, guidance will be critical in ensuring the quality of the final guidance.

As FDA continues on their task of completing this work, we would strongly suggest that FDA engages industry where additional feedback, clarifications, or discussions are needed. PQRI could again be utilized to rapidly resolve any particularly difficult issues.

Sincerely,

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Attachment: Comment Grid

2003D-0382 C29

Line Ref.	Comments
105	**Comment 1**: The draft guidance reads, "This guidance updates the 1987 guidance...." This document should be stated as replacing not updating the 1987 guidance.
147	**Comment 2**: The draft guidance reads, "An ISO 5 particle concentration is equal to Class 100 and approximately equals EU Grade A." Intermingling classification standards and by inference the testing requirements leads to confusion. For example, Class 100 is based on sampling air by the cubic foot (CF) where as ISO 5 is based on cubic meters (CM). Is it to be assumed that the Guidance will allow an area to be classified as ISO 5 if the specific testing required by the ISO standards is not done? Can data be extrapolated from CF to CM even though the total volume of air required to be tested under the ISO standards was not, in fact, tested?
167	**Comment 3**: The draft guidance reads, "Particles are significant .....by acting as a vehicle for microorganisms...." It is generally considered that particles 5.0 micron or larger can act as fomites. However, in the Contamination Control Manual JPG 5322.1 November 2000 (NASA) it is stated that " Counts <5.0 u> below 10 particles per cubic foot are unreliable except when a large number of samples are taken." In regards to microbial contamination it is not appropriate to link particulate results alone with microbial contamination. Recommend removing this statement from the guidance.
177	**Comment 4**: The draft guidance reads, "Deviations from this critical area monitoring parameter should be documented as to cause and significance." This cannot be complied with consistently. The root cause of a microbiogical contamination that is found at a low rate can rarely be identified and as such neither can the actual significance of the excursion. **Alternative Text:** Deviations from this critical area monitoring parameter should be investigated.
183	**Comment 5**: The draft guidance reads, "Nonviable particle monitoring with a remote counting system is generally less invasive than the use of a portable..." This sentence is too prescriptive and should be deleted. We are not aware of any published study supporting the claim made regarding remote systems. Portable systems continue to have an important role.
192 338	**Comment 6:** The term "certification" is used inconsistently throughout the document. This term is used associated with qualification, classification and certification.
217	**Comment 7**: Supporting Clean Areas. Regulatory agency concerns beginning in England have addressed cooling zones for autoclaved materials and suggested that these be Grade A for both viable and non-viable particulates. The original MHRA concern was that liquid materials would draw a vacuum as they cooled and could thus be contaminated by drawing in surrounding air. Obviously this is not an issue with wrapped, non-liquid items. A statement should be included in the guidance addressing this issue and specifying appropriate environmental conditions be supplied for cooling autoclaved materials. This should further state that Grade A requirements apply specifically to unwrapped and liquid materials but other standards may be satisfactory for wrapped, non-liquid items.
293	**Comment 8**: The draft guidance reads, "Among the filters that should be leak tested are those installed in dry heat depyrogenation tunnels commonly used to depyrogenate glass vials." Leak testing of filters installed in dry heat depyrogenating tunnels is technically problematic. Once the filters are "burned in"they do not have the same physical characteristics when operating at a cooled state, so testing them when in the cooled state is not a good representation of how the filter is functioning at temperature. Filter manufacturers do not recommend testing at high temperatures for safety reasons -- the materials used to do so are often toxic when exposed to heat, generating irritating and noxious vapors. Additionally, the flash point of such materials is around the temperature of the tunnel, raising other safety is-

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	sues. **Alternative Text:** Filters should be integrity tested prior to installation and prior to disposal as part of a preventative maintenance program. They should also be regularly monitored in use for viable and non-viable particles. Any excursions in monitoring should prompt an investigation that might include integrity testing.
312	**Comment 9:** The draft guidance reads, The Institute of Environmental Sciences and Technology recommended practice is use of a DOP concentration of 10 – 100 micrograms/liter as documented in IEST-RP-CC006.2, "Testing Cleanrooms". The designation of a specific agent and the proposed 25 – 100 micrograms/liter is too restrictive. **Alternative Text**: "a challenge should introduce the aerosol upstream of the filter in a concentration sufficient to detect leaks at the filter's designed airflow"
331	**Comment 10:** The draft guidance reads "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." Velocity "at a defined distance proximal to the work surface" is too vague to implement. The closer you get to any equipment or surface the more variable the data will be due to air changing direction due to influences of the surfaces, i.e. flat surface bounce back or proper flow away from product. Whatever location is chosen should be used over time so that velocity comparisons could be reasonably made. The requirement for measurements at the work surface should be removed. **Alternative Text**: Airflow velocities are measured 6 inches from the filter face for HEPA filters in the critical area."
373	**Comment 11**: The draft guidance reads, "To prevent contamination, partially closed sterile product should be transferred only in critical areas. 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)" is too restrictive and does not recognize the potential use of newer technologies such as appropriately designed and validated transfer carts. **Alternative Text:** To prevent contamination, partially closed sterile product should be transferred under class 100 conditions or through the use of validated transfer systems specifically designed to prevent contamination.
442	**Comment 12**: The draft guidance reads, "Between uses, instruments should be placed only in sterilized containers. Instruments should be replaced as necessary throughout an operation." This statement is too specific in that there are several ways in which instruments can be handled to maintain their sterile integrity. One such example would be placing them on a sterilized surface within a class 100 environment. **Alternative Text**: Between uses, instruments should be placed only in sterilized containers or on a sterilized field.
493	**Comment 13**: The draft guidance reads, "Semi-annual or yearly requalification is sufficient for automated operations where personnel involvement is minimized." The frequency of the requalification should be a function of the micro history of the process and personnel involved. Semi-annual requalification is not necessary when an effective personnel monitoring program is in place. As a guidance, annual requalification is sufficient unless there is substantial and broad data to the contrary.
535	**Comment 14:** The draft guidance reads, "A drug product produced by aseptic processing can become contaminated through the use of one or more components (e.g., active ingredients, excipients, Water for Injection) that are contaminated with microorganisms or endotoxins. It is important to characterize the microbial content of each component that could be contaminated and establish appropriate acceptance limits based on information on bioburden. Knowledge of bioburden is critical in assessing whether the sterilization process is adequate."

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	Although it is acknowledged that periodic characterization of microbial content of each component is important, routine bioburden testing of each formulated solution prior to sterile filtration is more critical in understanding the bioburden load being applied to the filer. Rather than focusing the guidance on the bioburden of each component the guidance should focus on the bioburden of the formulated solution prior to filtration.
564	**Comment 15:** The draft guidance reads "Parenteral products are intended to be nonpyrogenic. There should be written procedures and appropriate specifications for acceptance or rejection of each lot of components that might contain endotoxins." Few components (actives and excipients) used in parenteral products are derived from sources liable to be endotoxic, such materials of natural origin, starches sugars etc., but are chemically synthesized and therefore are of low natural bio/endo – burden. An assessment should be performed on each component and in cases where the potential for contamination with endotoxin exist testing should be performed on each lot. **Alternative 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 for 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.
565	**Comment 16**: The draft guidance reads, "There should be written procedures and appropriate specifications for acceptance or rejection of each lot of components that might contain endotoxins" Guidance should be provided regarding the requirement that products must meet their release criteria for pyrogen or endotoxin levels. The firms should be given the latitude to develop the required level of ingredient and in-process testing required. **Alternative Text**: Incoming components (ingredients) should be accepted according to specifications included in the regulatory submission. Any components failing to meet defined specifications should be rejected.
722	**Comment 17**: The draft guidance reads, "Media fill studies should simulate aseptic manufacturing operations as closely as possible, incorporating a worst-case approach." The use of "worst-case" is not appropriate. Stacking all potential worst-case situations into each media run does not represent an appropriate challenge simulating normal processing. **Alternative Text**: Media fill studies should simulate aseptic manufacturing operations as closely as possible. Media fill studies should be designed to address applicable issues such as:
727-743	**Comment 18**: Media fills should be designed to represent (mimic) the filling operation. The text in the dot point "number and type of normal interventions, atypical interventions, unexpected events (e.g., maintenance), stoppages, equipment adjustments or transfers" should not specify "number" Number of typical interventions is proportional to the length of the operation. The term "Unexpected" should be clarifired. The text in the dot point "operator fatigue" is unnecessary to be addressed during a normal media fill and should be deleted. Environmental and personnel monitoring is a better assessment of operator fatigue; this should not be required for media fill.
780	**Comment 19**: The draft guidance reads "The duration of aseptic processing operations is a major consideration in determining the size of the media fill run. Although the most accurate simulation model would be the full batch size and duration because it most closely simulates the actual production run, other appropriate models can be justified" This statement is inconsistent with other areas of the document and indicates that the larger the media fill is the more validity the media fill has. Elsewhere in this section the FDA specifies media fill sizes that are not

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	representative of production duration. This sentence is not consistent with PQRI recommendations on the 'Concept Paper' or PDA Technical Documents. The duration of the process simulation should be dictated by the time needed to prepare the required number of units and to include the activities to simulate necessary interventions. This statement should be deleted from the guidance.
815	**Comment 20**: The draft guidance reads, "Some batches are produced over multiple shifts or yield an unusually large number of units, and media fill size and duration are especially important considerations in the media fill protocol. These factors should be carefully considered when designing the simulation to adequately encompass conditions and any potential risks associated with the larger operation." This statement infers that batches with larger numbers of units require media fills with larger number of units. The number of units to be filled during a media fill should be set based on the number of units required to incorporate the items identified in the study design. This statement is in conflict with the earlier statement in this section that provides acceptable starting points for the number of media fill units needed.
822	**Comment 21:** The draft guidance reads, "The media fill program should adequately address the range of line speeds (e.g., by bracketing all vial sizes and fill volumes) employed during production. Each individual media fill run should evaluate a single worst-case line speed, and the speed chosen for each run during a study should be justified. For example, use of high line speed is often most appropriate in the evaluation of manufacturing processes characterized by frequent interventions or a significant degree of manual manipulation. Use of slow line speed is generally ..." The statement is contradictory with one sentence states that the range of speeds should be addressed, while the other specifies "worst case". **Alternative Text**: The media fill program should address line speed (e.g., by bracketing all containers) employed during production. During the media fill a single or multiple line speeds may be used. The speed or speeds chosen for each run during a study should be justified and documented.
837	**Comment 22**: The draft guidance reads "To the extent standard operating procedures permit stressful conditions, it is important that media fills include analogous challenges to support the validity of these studies" is unnecessary and overly strict. This statement is unnecessary and overly stringent. The statement may lead to misinterpretation and to an expectation that HVAC systems may be expected to be operated at their worst case conditions e.g. high humidity, low differential pressure and low air exchange rate. The purpose of a media fill is not to validate the HVAC system, that is undertaken as a separate exercise. The purpose of a media fill is to ensure the critical interface of human operator and aseptic filling equipment can maintain an acceptable level of aseptic process integrity. **Alternative Text:** To the extent standard operating procedures permit stressful conditions, e.g. maximum number of personnel present and elevated activity level, it is important that media fills include analogous challenges to support the validity of these studies. Stressful conditions should not include reconfiguration of HVAC systems to operate at worst case limits.
877	**Comment 23:** The draft guidance reads, "Each media-filled unit should be examined for contamination by personnel with appropriate education, training, and experience in microbiological techniques." Initial examination of filled units does not require education, training or experience in microbiological techniques. Training and experience in examination/inspection of filled units and growth patterns of microbiological organisms is required. Requiring microbiologists to perform the initial inspection is unnecessary and should be removed. The firm should have a detailed training program.
897	**Comment 24**: The draft guidance reads, "The ability of a media fill run to detect potential contamination from a given simulated activity should not be compromised by a large-scale line clearance, which can result in removal of a positive unit caused by an unrelated event or intervention".

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	This statement is contradictory and should be deleted. The expectation is that the media fill simulates the manufacturing process. Elsewhere the guidance specifies that specific procedures for removal of units in production should be duplicated in process simulation.
920	**Comment 25:** The draft guidance reads "The microorganisms should be identified to species level" This statement is to specific. It may not be possible to identify microorganisms to the species level. **Alternative Text**: The microorganisms should be identified to species level, *if possible*
Foot-note 9	**Comment 26**: The draft guidance states "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." is not consistent with other sections of the document. The expectation is that the media fill simulates the manufacturing process. Incubating units normally discarded does not follow this basic assumption and provides no data regarding the acceptability of the media fill. This statement should be discarded.
1033	**Comment 27**: The draft guidance reads, "Those surfaces that are in the vicinity of sterile product or container closures, but do not directly contact the product should also be rendered sterile where reasonable contamination potential exists." This statement is not appropriate. Surfaces in the vicinity of sterile materials should not be required to be sterilized unless there is direct contact. The statement should be deleted.
1062	**Comment 28**: The draft guidance reads, "D-value of the biological indicator can vary widely depending on the material to be sterilized." This is an incorrect use of the term D-value. The D-value does not vary based on the material to be sterilized but rather the D-value may very based on the carrier used.
1073	**Comment 29:** The draft guidance reads, "The formal program providing for regular revalidation should consider the age of the sterilizer and its past performance." "age of sterilizer" should be removed from the statement. The decision to requalify is not age dependent.
1114	**Comment 30**: The draft guidance reads, "Temperature monitoring devices for heat sterilization should be calibrated at suitable intervals, as well as before and after validation runs." It is unclear from this statement whether the requirement for calibration before and after validation runs is in reference to thermocouples used for the validation study or temperature controllers (thermocouples and/or RTDs) for the sterilizer itself. If the reference is to the latter, recalibration before/after validation runs is excessive and unnecessary. The statement should be clarified and if the reference is to the temperature controllers for the sterilizer itself it should be deleted.
1117	**Comment 31**: The draft guidance reads, "The microbial count and D-value of a biological indicator should be confirmed before a validation study." If using a commercially prepared BI with a certified D-value from an audited and approved vendor repeat confirmation of the D-value should be unnecessary. The statement should be deleted.
1229	**Comment 32:** The draft guidance reads "Upon preparation, disinfectants should be rendered sterile, and used for a limited time, as specified by written procedures" This could be read as requiring sterilization post preparation. This would effectively eliminate a common industry practice of purchasing sterile concentrated solutions and preparing aseptically. The statement also does not take into consideration self sterilizing agents that would not require sterilization. **Alternative Text:** Disinfectants should be purchased sterile, aseptically prepared from sterile concentrated

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	solutions or subject to filter sterilization. It is not generally required to filter sterilizing sporicides.
1292	**Comment 33**: The draft guidance reads, "At minimum, the program should require species (or, where appropriate, genus) identification of microorganisms in these ancillary environments at frequent intervals to establish a valid, current database of contaminants present in the facility during processing (and to demonstrate that cleaning and sanitization procedures continue to be effective)." The current text indicates that at a minimum the EM program should ID isolates from the less controlled environments, such as Class 100,000 (ISO 8) areas, to the species (or, where appropriate, genus) level at frequent intervals. The level of identification should be changed from identification to the species (or, where appropriate genus level) to "characterization." The requirement for a EM program that requires frequent identification of isolates from less controlled environments, such as Class 100,000 (ISO 8) areas, to the genus and species level is to great when evaluating the usefulness of the data obtained. Morphologically representative environmental monitoring isolates from lesser controlled environments, such as Class100,00 (ISO 8) areas, should be characterized. This pertains to the detection of isolate types obtained from samples that breach the action level as well as the periodic characterization of isolate types below the action limit. The information gathered from this activity is helpful in understanding the general types of organisms present and if the cleaning program needs to be adjusted. The intense amount of resources required to ID to the genus/species level does not provided added value in these areas over general characterization. The focus of genus/species identification should be placed on the samples taken closer to the aseptic operation. **Alternate Text:** At a minimum the program should require morphologically representative environmental monitoring isolates to be characterized. This pertains to the detection of isolate types obtained from samples that breach the action level as well as the periodic characterization of isolate types below the action limit.
1297	**Comment 34**: The draft guidance reads, "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." Definitions are needed for "Rapid genotypic methods" and "phenotypic techniques" used in this statement. While these methods are fine, biochemical, fatty acid methyl ester and other methods currently employed are fit for purpose. The level of organism identification produced by current ID methods provides the information necessary for effective trending of contamination, product failure investigations and other studies. This statement should be deleted from the guidance.
1305	**Comment 35**: The draft guidance reads, " Total aerobic bacterial count can be obtained by incubating at 30 to 35°C for 48 to 72 hours. Total combined yeast and mold count is generally obtained by incubating at 20 to 25°C for 5 to 7 days." As written this statement may inhibit the use of advanced technologies.
1339	**Comment 36**: The section entitled "XI. Sterility Testing" is not appropriate to be included in this document. Sterility testing is a USP compendia test method and as such is presented in the USP. This is a legally binding test and as such any added specificity need in the test should be included in the USP. The EP and USP methods are now harmonized. Including information in this guidance on the methods performance increases the risk of inconsistencies developing. The section should be deleted. The detailed information regarding the investigation of sterility testing failures was found to be very helpful and should be considered for submission to the UPS sterility testing section.
1395	**Comment 37**: The draft guidance reads, "the batch processing circumstances – samples should be taken in

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	conjunction with processing interventions or excursions" There is insufficient justification of the value in taking additional sterility samples for each intervention. It would be impractical, especially when there is media fill data to support the intervention.
1510	**Comment 38:** The draft guidance reads, "All in-process data must be included with the batch record documentation in accordance with section ." Raw data might not always be part of the batch documentation. In several areas (i.e. EM, Water monitoring results) the data may be located in systems where a review is done prior to batch release. **Alternate Text:** All in-process data must be reviewed prior to batch release.
1546, 1556, 1682	**Comment 39:** An isolator is a positive pressure enclosure designed to maintain a higher pressure then the surrounding areas. This is analogous to a traditional clean room, where by the room pressure is higher then the areas surrounding it. A leak in the isolator or components does not automatically constitute a "significant breach" due to the positive pressure in the isolator system. The advantage of an isolator, is the removal of all direct human interaction from the product and process. A well designed maintenance program is the critical requirement to assure the isolator and components do not degrade and go unnoticed. The guidance should be revised ti indicate that a Breaches of integrity should be investigated and If it is determined that the product has been compromised, appropriate action taken.
1815-1825	**Comment 40**: Typo "sterilyzed" should be "sterilized"