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Wyeth Pharmaceuticals

Date: November 4, 2003

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Re: Docket No. 2003D-0382: Draft Guidance for Industry on "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice"

Dear Sir/Madam:

Wyeth Pharmaceuticals is submitting written comments on the draft guidance for industry entitled, "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (August 2003)."

Wyeth is one of the world's largest research-based pharmaceutical and health care companies. It is a leader in the discovery, development, manufacturing, and marketing of prescription drugs and over-the-counter medication, with leading products in women's health care, cardiovascular, central nervous system, anti-inflammatory, infectious disease, hemophilia, and oncology product categories, and is also a major manufacturer of preventative vaccines.

We are submitting the enclosed comments in duplicate. Wyeth appreciates the opportunity to comment on the above-mentioned draft guidance for industry, and trusts that the Agency will find these comments useful.

Sincerely,

Roy J. Baranello, Jr.
Assistant Vice President
Worldwide Regulatory Affairs

Attachment

2003D-0382 C26

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Docket No. 2003D-0382: Draft Guidance for Industry on "Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice"

General Comments:

1. A greater attempt should be made to harmonize the FDA guideline with European regulatory documents and international standards. Wyeth Pharmaceuticals, a global pharmaceutical company, manufactures and distributes sterile products internationally and needs to reconcile differing global requirements.
2. All measurements should be cited in both S.I. and U.S units.
3. Reference to values for space pressurization, air velocity, microbial counts, etc in the guideline may result in setting de facto requirements when aseptic processing facilities are too complex to set blanket requirements.
4. The document does not address risk assessment, especially with respect to contamination in environmental monitoring and sterility testing.

Specific Comments:
II. Background

B. Technical Framework:
Line 73: What is meant by "high quality" environment for terminally sterilized products? This should be defined in terms of a minimal classification such as Grade C or Class 10,000 cleanliness levels.

Line 74: The environment for filling and sealing injectable drug products manufactured using terminal sterilization needs to minimize particulate contamination as well as limit microbial contamination.

Line 83: What is meant by "extremely high quality" environment for aseptically filled products? This should be defined in terms of a minimal classification such as Grade A or Class 100 cleanliness levels where product and sterile packaging components are exposed to the controlled environment.

Line 96: Suggested revision - "Poor cGMP conditions can ultimately pose a life-threatening health risk to the patient, seriously damage the reputation of the manufacturer, and expose them to regulatory action."

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III. Scope

Line 114: The efficacy of heat treatment and the processing steps require further definition.

Is the use of adjunct heating steps for aseptically filled products being made a requirement or a consideration? Is there a burden of proof on the manufacturer to demonstrate that an adjunct-heating step is not compatible with the sterile drug product? If so, chemical stability of sterile drug products is favored by high temperature/short time treatments, not longer exposure to lower temperatures, and this treatment may require specialized equipment not currently employed in the pharmaceutical industry.

IV. Building and Facilities

Air Classifications

Line 142 Table: The air monitoring limits expressed in cfu/m3 differ from the recommended limits found in the ISO Standards and EU GMP regulations. In addition, the limits found in the EU GMP regulations specify at rest and in operation whereas all the non-viable air particulate levels are in the in operation mode. In the interests of harmonization, the ISO classifications, requirements and SI units should be employed throughout the document as well as the U.S. measurement units. Also, the microbiological limits are recommended guidance levels not specifications, so they should not be described as limits.

It is recommended that the units be used consistent throughout the table; they should be expressed in both cfu/ft^3 and cfu/m^3. Furthermore, the recommended level for air monitoring only has meaning when the volume of air sampled is specified.

A. Critical Area-Class 100 (ISO 5)

Line 173: This implies that a minimum of 1 cubic meter of air must be sampled at one location when taking a non-viable particulate count. Clarification is needed if this amount of sampled air is the total amount taken for one sample event in an area but not necessarily in one location at one time.

The document endorses remote non-viable particulate monitoring as less invasive and it is more compatible with periodic monitoring.

Line 175: Particulate monitoring not more than one foot from the work site is not a general industry practice. The sampling, if manual, may expose the product to potential microbial contamination or probes and the sampling process may disrupt the airflow patterns within critical areas. Also the equipment operation and routine processing steps may generate particulates contributing to a higher count when the air is sampled.

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Line 182: The statement "regular monitoring" does not indicate the frequency of particulate sampling. Every 30 minutes may represent an industry practice with the ability to take repeat samples if the measurement exceeds the alert or action level.

Line 198: Laminar flow patterns usually address the entire aseptic processing area and/or the aseptic processing core and not specific points of use. The use of segregating curtains or rigid barriers for the spot or localized protection of the aseptic processing core is a common practice and is supported in this guideline. Equipment and personnel within the unidirectional laminar flow will inevitably result in turbulence. The turbulence associated with personnel is readily restored to a unidirectional airflow when they move out of the critical area but equipment permanently sited above the product will create permanent level of turbulence. Some turbulence is acceptable as long as the airflow sweeps particles away from product contact surfaces and exposed product and sterile packaging components.

Footnote 4 in the draft guidance establishes the air velocity as 90-100 feet per minute when the industry practice is 90 feet per minute ± 20% (0.45 m per second ± 20%) at the HEPA filter face. However, the air velocity at a workstation should be sufficient to rapidly remove the most critical particle size range, i.e. skin particles 10-20 micron in diameter that bear bacteria, before they settle on surfaces or within exposed product and packaging components without creating excessive turbulence.

B. Supporting Clean Areas
Line 230: We recommend adding the line, "See Appendix 1 for Isolator Technology".

C. Clean Area Separation
Line 236: Pressure differentials of 10 – 15 Pascals should be referenced as well as the U.S. units of measurement, inches of water.

Line 243: Continuous monitoring of space pressurization seems excessive. Recording the space pressurization at the beginning and end of an aseptic processing operation would be sufficient. The cascade of space pressurization from the aseptic core to the surrounding support areas should be sufficient to prevent the ingress of particulates when the door is opened. Time delays may be employed to avoid alarms during routine operations that have been qualified during process simulation.

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Line 247: The number of minimal air changes for class 100,000 is listed here but not for Classes 100 and 10,000. It is recommended that the following ranges be added to the document: class 100,000, 10,000 and 100 (5 to 50, 50 to 100 and 250 to 500 changes per hour respectively). However, it should be noted that air changes are a function of room volume as well as air velocity. These ranges would be informational, not requirements.

Line 252: Alarms should be limited to total loss of space pressurization not pressure changes when doors are opened and closed. The use of interlocks should be employed to prevent both sets of doors being opened at the same time and to isolate rooms of different air cleanliness classification.

D. Air Filtration
Line 262: Microbial and particulate quality should be equal or better than the air cleanliness classification in the environment into which the compressed gas is introduced.

Line 272: This is not possible when solutions or materials are being added or withdrawn from the tanks, which is why a sterile vent filter is in place. Such a vent filter would prevent over-pressurization from occurring. Over pressurization of tanks is not an absolute requirement. Sterilized tanks or liquids may be held at ambient pressure and protected by a vent filter.

If this is intended only for "holding", then the additional manipulations to pressurize and subsequently vent pressure may raise the likelihood of contamination.

Line 277: Heated hydrophobic vent filters may be used on heated WFI storage tanks as well as compressed gas supply systems.

Line 283: The Title should be High Efficiency Particulate Air (HEPA) Filters. This section provides details relating to the aerosol used and the method of performing the leak test. If the objective of the guideline is to assure that the HEPA filters are tested regularly to assure that they are not leaking, and the criteria is that it should retain 99.97% of particulate greater than 0.3 micron in diameter, then it should simply state that. In this way, advanced technology can take place.

Line 302: What is the justification for the recommended particulate concentration in the DOP challenge? The efficiency test determines the rating of a filter while integrity testing evaluates the HEPA filter, frame and seal. This distinction needs to be better highlighted in the document.

Line 326: Is non-uniformity of air velocity across the filter a good measure of filter functionality? The pressure drop across the filter is a measure of the HEPA filter performance and the particulate counts indicative of filter leaks should be monitored in preference to air velocity.

E. Design
Line 344: Additional ways of minimizing microbial contamination, is to limit the conveyer length and increase the conveyer speed, to place the stoppering station immediately proximal to the filling station and limit interventions by operators.

Line 403. An absolute prohibition of drains in aseptic processing areas is not in keeping with industry practice. Drains should be absent from class 100 areas but would be present in class 100,000 equipment and packaging component preparation areas.

V. Personnel Training, Qualification, & Monitoring
A. Personnel
Line 445: We recommend adding the option of changing gloves to the phrase, "... gloves should be regularly sanitized or changed...."

Line 467: What evidence is available to support the belief that speaking adjacent to an aseptic filling line is not an acceptable practice?

VI. Components and Container/Closures
A. Components
Line 533: In this section, the only mention of irradiation is with respect to the sterilization of plastic containers. Irradiation deserves to be mentioned as a method of sterilization for components, containers and closures, and such a reference would allow advances in technology to take place.

Line 551: The emphasis in the pharmaceutical industry on overkill autoclave cycles, the complexity of autoclave validation and the potential larger lot sizes with an aseptic filling operation all contribute to the decision to implement aseptic processing and not terminal sterilization.

VII. Time Limitations

Line 675: There is a danger that holding times are driven by scheduling and not sterility assurance. In practice it is difficult to justify the hold time of sterilized equipment and packaging components. Validating the holding time through process simulation using media fill is problematic while integrity testing wrapping and seal containers typically involves microbial challenges many magnitudes higher than that the equipment is exposed to in the clean room.

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IX. Validation of Aseptic Processing and Sterilization
A. Process Simulation
Line727: What are "normal interventions and "atypical" interventions? These are not defined clearly. Line 712 refers to "manipulations". This term is not defined either. Manipulations should be defined as manual activities associated with the actual process. Interventions are performed to correct occurrences that are not part of the process (e.g., correcting a vial jam), normal interventions occur with each run and atypical interventions do not.

Line 746: We agree that media fills should not be used to support questionable practices. However, when do worst-case situations end and questionable practices begin? Including examples of questionable practices in the guidance would be helpful.

Line 783: The duration of the media fill should adequately mimic worst case conditions and cover all manipulations without being the same run size as the production fill. There is a tension between the concept of using the worst-case conditions and not attempting to validate unacceptable practices.

Line 823: Media fills should bracket all vial sizes and fill volumes employed during production and not just the worst case.

Line 833: With environmental controls of airflow velocity, temperature, relative humidity and space pressurization it is impractical to include the extremes within the process simulation.

Line 847: Growth promotion requirements should be spelled out. Growth promotion testing should reflect the incubation conditions used for the media fill.

Line 909: The guidance should give more information for the expected accountability of prepared vials at the end of the media fill.

Line 920: Add, "where possible" to "identified to species level". Sometimes it is just not possible with current microbial identification systems. For example, the Vitek Microbial Identification System typically has a first pass identification success of around 75%. In most investigations the identity of the isolate is used to postulate the origin of the microorganism. For example, Bacillus spp. is assigned as airborne while Staphylococci are assigned as from human skin. Whether the isolate is identified to species or genus may not add to the investigation. If the isolate needs to be traced from the manufacturing environment to the product, the biochemical reaction pattern may be used in place of the species identity.

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Line 935: The statement that the number of contaminated units should not be expected to increase with the number of vials filled is not compatible with the existence of contamination rates. The FDA emphasis has been on situational contamination such as failure of aseptic technique during the process. The EU and ISO approach is statistical and recognizes that there is a low but discernable contamination rate in clean rooms. The EU and ISO approach has led to the acceptance criterion for process simulations of a target of zero contaminated units but not more than 0.1% contamination rate.

Line 937: Is this a recommendation to fill 10,000 for a media fill with the acceptance criterion no more than one turbid filled container? This may be too long a media fill for routine process simulations. What happened to the E.U. acceptance criterion of not more than 0.1% contamination rate at the 95% confidence level and filling 4750 units to make this statistical claim?

C. Sterilization of Equipment and Container and Closures
Line 1031: Requiring that surfaces in the vicinity of sterile product or packaging components be rendered sterile is a departure from industry practice and is not achievable. A clean room is a controlled environment not a sterile environment.

Line 1044: Suggest rephrasing, "... adherence to strict aseptic methods within a controlled environment."

Line 1054: Most modern autoclaves have the capacity for pre-vacuum cycles so that air pockets within the autoclave chamber is not an issue.

Line 1096: The sterilization of in-line filters is a steam-in-place (SIP) issue. The document should have a section specifically addressing SIP issues.

Line 1114: This section provides 6 examples of devices that need to be maintained in a calibrated state. By providing such a list, there is a risk that crucial devices may be ignored. It may be more appropriate to state that devices used to make quality decisions are maintained in a calibrated state.

X. Laboratory Controls
A. Environmental Monitoring
Line 1151: Air, surface and personnel monitoring methods are considered standard methods and as such need not be validated but qualified for their intended use.

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Line 1154: The monitoring of product-contact surfaces as "critical surfaces" has been recognized to include product-container and closure contact surfaces such as filling needles and the inside of stopper bowls. We consider the monitoring of key indicator sites in the clean rooms during product operations to be a more meaningful determinant of effective clean room control than direct monitoring of product-contact surfaces. Key indicator sites are locations chosen to represent known microbial "worst-case" locations and/or areas of high operator activity. Due to their proximity to personnel activity, indicator sites have a higher potential for operator contamination than sterilized surfaces in the critical clean zone. We recommend the removal of the words, "including the critical surfaces that come in contact with the product, containers, and closures".

Line1178: What are "false negatives" with respect to environmental monitoring? Is this intended to mean microorganisms were present in the sample but were not enumerated or were present in the environment but not sampled? The use of the term "false negatives" in this context is not recommended.

Line 1193: The draft document does not provide sufficient guidance in the area of trending of environmental monitoring results. The alert level may be used for trending purposes. Possible rules that could be applied include the frequency of alert level events within a specified time interval, i.e., quarterly, monthly or weekly, the time between alert level events where a decline in time between events may indicate a loss of environmental control, no change a maintenance of control and an increase in time between events an increase in environmental control, and the occurrence of consecutive alert levels within a clean room and/or location which would statistically be an unlikely event.

Line 1205: The guidance document does not allow the averaging of environmental monitoring results but the EU annex does.

Line 1212: Products, but not lot, may generate trend reports.

Line 1222-1239: We recommend that "Sanitization" be changed to "Disinfection", and that "disinfection" be defined in the glossary to include "chemical agent that destroys vegetative organisms". We also recommend use of sterile disinfectants in critical areas and support, not 100,000 and unclassified. We also recommend adding that all disinfection equipment needs to be sterilized prior to use. Sporicidal agents should be used periodically, as part of a routine regimen, and are not necessary for all disinfection performed, as long as the cleaning data demonstrates that spore formers are being controlled. 70% Isopropanol is a sanitizing agent, not a disinfectant.

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Line 1226: Demonstrating sanitizer efficiency by sampling before and after sanitization is an ineffective approach when the vast majority of samples are zero. The sanitizer efficiency is best established in laboratory studies and confirmed during routine surface monitoring.

Line 1238: Please clarify what specific provisions in the environmental monitoring should be used to assess sanitization efficacy. Representative environmental monitoring isolates should be periodically used to demonstrate disinfection efficacy. Organisms associated with adverse trends may be investigated as to their sensitivity to the disinfectants employed in the clean room where they were isolated.

Line 1241: There is no mention of anaerobic monitoring in this section. It should be addressed.

Line 1255: The most common type of air sampler employed in the pharmaceutical industry is the sieve impactor. This section could be re-written and the PDA Technical Report #13 cited.

Line 1273: All types of methods used for environmental monitoring should be qualified, not just passive air monitoring. The exposure of air settling plates for periods up to 4 hours is well established.

B. Microbiological Media and Identification
Line 1297: The endorsement of genotypic microbial identification over phenotypic is not justified. Phenotypic microbial identification methods are industry practice for routine identification of microorganisms isolated during the monitoring of components, the manufacturing environment and product. We believe that phenotypic methods should be retained for routine identification. Although genotypic methods may be more reliable and less subjective, they are more technically challenging and expensive and their use should be limited to critical investigations associated with direct product failure.

Line 1300: The goal of microbial monitoring is to consistently detect and enumerate microorganisms.

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Line 1305-06: The guidance is not clear on whether the incubation condition of 30-35°C followed by 20-25°C is the same sample, or is the guidance inferring the use of two sets of samples or different types of media? TGA is a general medium that is capable of supporting both bacteria and fungi. A combined incubation process using a single medium, TGA, is a typical practice and should be endorsed by the guidance.

These incubation temperatures do not take thermophiles into account.

Lines 1311-12: The addition of deactivating agents is specific to surface monitoring media and should be addressed under the section for surface monitoring.

C. Prefilitration Bioburden
Line 1314: The bioburden challenging the sterilizing filter would be more conditional on the bulk volume and the filter size than the product. The guidance over emphasizes toxiogenic materials derived from the pre-sterile filtration bioburden.

Line 1316: The bioburden necessary to contribute toxins in sterile products is 3-4 magnitudes higher than the bioburden limits set for sterile filtration. If you control the bioburden to maintain the required sterility assurance for sterile filtration, toxin production is not an issue.

Line 1318: Please clarify why bioburden limits are needed for individual products when the limits are related to filter surface area, bulk solution volume and filtration duration.

E. Particle Monitoring
Line 1331: Particulate deviations are probably caused by equipment operation, processing activities and personnel interventions so they may not require routine investigation and corrective action. An example may be recharging a stopper hopper that creates particulates; an activity included as a routine intervention during media fills but may trigger alert or action levels of particulates.

XI. Sterility Testing
Line 1352: Sterility test failure rates less than 0.1% have been routinely achieved using direct inoculation and membrane filtration methods in classical laminar flow hoods. The advantage of the use of an isolator over classical methods is the elimination of false positive test results and directing attention to manufacturing investigation in response to sterility test failures.

A. Choice of Methods
Line 1363: The compendial Bacteriostatis and Fungistasis (B&F) testing acceptance criteria are based on shorter incubation periods than 14 days. The acceptance criteria are copious growth within 3 days of incubation for bacteria and 5 days of incubation for fungi. The B&F test does not require that the recovery from the inoculated controls and product samples are comparable throughout the incubation period as is recommended. We recommend the removal of the words, "throughout the incubation period".

D. Sampling and Incubation
Line 1383: Sterility tests can detect low levels of contamination. The assumption is that a sterility test will detect a single viable microbial cell. The Bacteriostasis and Fungistasis Testing used to qualify the use of a sterility test with a particular product routinely uses inocula levels of 10-100 cfu confirming the sensitivity of the test. We recommend this be changed to, "Sterility tests are limited in their ability to detect low frequencies of contamination because of the small sample size".

Line 1395: Samples for sterility testing are usually taken using a stratified random sampling plan from the beginning, middle and end of the fill. Filled containers associated with interventions or excursions that are qualified by media fill would be retained in the lot. Other interventions that potentially lower the sterility assurance should be subject to line clearance and be discarded. The industry validates aseptic processing using process simulation and not by sterility testing product. We recommend removal of the words, "samples should be taken in conjunction with processing interventions or excursions."

E. Investigation of Sterility Positives
Line 1440: Sterility failures are typically too infrequent to identify trends. However, every failure should be intensively investigated. To use an analogy, with extremely rare events like plane crashes the cause of the failure leading to the crash is usually unique and will not represent a trend. The same is usually true for sterility test failures.

Line 1466: This section overestimates the value of trend analysis.

Line 1487: Facility construction and schedule maintenance should be considered in failure investigations as they have been found to be sources of adverse microbial trends in aseptic processing areas.

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XII. Batch Record Review: Process Control Documentation

Line 1516-7: Line clearance should be preferable to increased documentation and retaining potentially compromised filled containers in the manufacturing lot.

Appendix I: Aseptic Processing Isolators
A. Maintenance
Line 1565: We question whether sanitization of the interior of gloves used in isolator systems is industry practice. If the gloves develop a leak it will compromise the lot whether or not the glove interior is sanitized. Furthermore, most disinfectants are ineffective against spores and the use of a sporicidal agent would attack the material of construction of the gloves and be a safety hazard to the wearer of the gloves.

B. Design
Line 1611: The requirement for the interior of isolators to meet class 100 standards is difficult to support. With the separation of people from the aseptic process, meeting many physical parameters of a class 100 area, i.e., laminarity and air velocity, would seem unnecessary.

Line 1614: An isolator can be located in an unclassified room if the isolator is used for testing purposes only. The area minimally should have limited access.

D. Decontamination
Line 1654: This discussion should extend to the decontamination of conveyer belts.

F. Environmental Monitoring
Line 1700: Why monitor exit ports when we can monitor locations were sterile product and packaging components are exposed.

Appendix 3: Processing Prior to Filling and Sealing Operations
Line 1810, Appendix 3: There is insufficient guidance given to processes that occur in sterile biofermenters and bulk processing tanks.

A. Aseptic Processing from Early Manufacturing Steps
Line 1851: The authors believe that the transportation of bulk materials should be validated separately from aseptic filling operations.

Line 1855: Because the risk with the bulk process is considerably lower than aseptic filling, process simulations should be performed annually and not semi-annually.