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August 31, 2014

Ref: Docket FDA-2014-D-0779, "Draft Guidance for Industry on Current Good Manufacturing Practice — Interim Guidance for Human Drug Compounding Outsourcing Facilities under Section 503B of the FD&C Act; Availability"

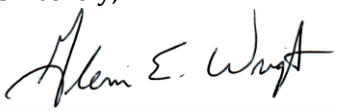
PQRI welcomes the opportunity to provide comments on the recent draft FDA Guidance for Industry entitled "Current Good Manufacturing Practice – Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act." Based on the impact that Drug Compounding Outsourcing Facilities have on patients throughout the US we commend FDA for their efforts to create such guidance.

The following comments were prepared by a PQRI comment group made up of industry experts in the field of pharmaceutical manufacturing and aseptic processing. The comment group included:

Fredrick Ayres, Eli Lilly and Company
Russell Madsen, The Williamsburg Group
Jean Poulos, Aceto Corporation
Edward Tidswell, PhD., Baxter Healthcare Corporation
Glenn E Wright, Eli Lilly and Company

If there are any questions please do not hesitate to contact PQRI at the number above.

Sincerely,



Glenn E. Wright
Manufacturing Technical Committee Member, PQRI

Guidance for Industry

Current Good Manufacturing Practice - Interim Guidance for Human Drug Compounding Outsourcing Facilities Under Section 503B of the FD&C Act

DRAFT GUIDANCE

Comments

#	Line	Comment
1	99	*"Sterile drugs should be produced only in ISO 5 or better air quality (see Table 1)."* - In the sentence "Sterile drugs" should be replaced with "Aseptically produced drugs." Drugs that are rendered sterile by processes such as autoclaving or irradiation are not required to be produced in ISO 5 or better environments.
2	99	*"Sterile drugs should be produced only in ISO 5 or better air quality (see Table 1)."* - Clarification is required, is this within ISO5 compliant air quality or an ISO5 classified and controlled area? Line 99 states ISO5 air quality, later (line 108) states ISO 5 zone (or critical area).
3	104	*Table 1* - As FS209E has been retired it should not be included in the table.
4	112	*"The air cleanliness classification of the area surrounding the ISO 5 zone immediately adjacent to the aseptic processing line should meet, at a minimum, ISO 7 (Class 10,000) standards"* - Clarification is required, is this within ISO7 compliant air quality or an ISO7 classified and controlled area?
5	115	*"If an isolator is used, the surrounding area should meet at least ISO 8 (Class 100,000) standards."* - Is this ISO 8 air cleanliness or an ISO 8 classified and controlled area?
6	126 And 903	*"…air control (e.g., non-laminar, turbulent")* - The term laminar/laminarity is not technically appropriate, unidirectional should be used.
7	127	*"HEPA periodic testing/recertification should be performed at least twice a year …"* - What is the rationale for this frequency?
8	127-129	*"HEPA periodic testing/recertification should be performed at least twice a year to ensure that appropriate air flow and quality is maintained. These tests should include integrity testing of the HEPA filters, particle counts, and air velocity checks*." – Test acceptance criteria/acceptable values should be stated. Additional details concerning the particle counting locations, numbers etc. should be included. - HEPA filters are not "integrity tested." The correct terminology is

		"leak tested." The term “integrity testing” in the sentence should be replaced with “leak testing.”
9	130-131	*“Velocities of unidirectional air should be measured six inches from the HEPA filter face and at a defined distance close to the work surface in the ISO 5 area.”* - Test acceptance criteria/acceptable values should be stated when measured six inches from the HEPA filter face.
10	133	*“If any portable ISO 5 units are moved from one location to another, re-qualification should be performed before resuming sterile compounding in the unit.”* - The term “sterile” should be replaced with “aseptic.” - This requirement should also include an evaluation to determine if requalification of the area as well as the portable ISO 5 unit.
11	142	*“To prevent contamination or mix-ups during the course of sterile and other operations”* - The term “sterile” should be replaced with “aseptic.”
12	153-163	*“Pressure differential limits should be established, and control systems should include built-in alarms to detect excursions. Monitoring for pressure differentials, humidity, and temperatures should occur during production, and prompt action should be taken to correct inappropriate conditions. If a problem cannot be immediately corrected, production should stop until corrected.* *Monitoring procedures should require documentation and investigation of any instances in which there is a loss of positive pressure in the clean room during actual production, the lots affected, and the corrective action taken. System alarms may not be necessary if differentials are regularly checked during operations (checks should be scheduled considering the environment, such as use of an isolator versus a less protected process) and the results recorded in logs and evaluated against pre-specified alert and action limits at each check.”* - These two paragraphs are contradictory. Based on the criticality of proper pressure differentials alarms should be required.
13	168	*“For penicillin/beta-lactam products, a separate facility (or physically separate space) is required (see § 211.42(d)).”* - If a physically separate space is used rather than a separate facility other appropriate controls related to equipment, product, and people must be in place to prevent penicillin contamination of non-beta-lactam products.

14	184-186	*"Procedures should describe the methods and schedule for cleaning and include the use of sporicidal disinfectants in the ISO 5 area and classified rooms on a regular basis."* - In this sentence the term "regular basis" is too vague and should be replaced with "regular predefined basis."
15	188	*"The suitability, efficacy, and limitations of the disinfecting agents being used should be monitored."* - These are broad terms which require more specific description, definition or appropriate reference. For example suitability versus surface compatibility, or efficacy assuring an appropriate log reduction or control of the anticipated microflora.
16	216	*"Include at least daily monitoring of the ISO 5 zone during operations"* - As the compounding operation could occur across more than one shift, daily monitoring in such cases would not be sufficient. Monitoring should be performed for each shift during compounding operations.
17	222	*"- Be supported by an evaluation of the choice of the sampling locations and sampling methods"* - A technical evaluation based upon risk and peer reviewed information should be required for sampling methods. This should also extend to the scientific justification for choice of culture media and incubation conditions.
18	262-270	*"The Agency does not intend to take action against an outsourcing facility regarding the identification or testing of each lot of single-use equipment, containers, and closures if (1) for a finished drug product intended to be sterile, the supplier certifies and labels the material as ready-to-use, sterile, non-pyrogenic; (2) the supplier's packaging integrity is verified upon receipt before use; and (3) the certificate of analysis (COA) provided by the supplier is reviewed to verify that the product is represented to meet the required specifications established by the outsourcing facility, including sterility and depyrogenation. Any single-use equipment, container, or closure not meeting acceptance requirements must be rejected or not used until rendered suitable for use (see §§ 211.84(d), (e) and 211.67(a))."* - The outsourcing facility should ensure the supplier has validated the sterilization and depyrogenation processes used, as this has a direct impact on the sterility of the product. - To ensure the proper verification of the supplier's packaging integrity a requirement that a formalized inspection process with specific instructions for each packaging configuration received should be included.
19	268-270	*"Any single-use equipment, container, or closure not meeting acceptance requirements must be rejected or not used until rendered suitable for use (see §§ 211.84(d), (e) and 211.67(a))."* - This statement appears to be out of place as materials that are

		provided by a supplier that do not meet the acceptance requirements should be rejected as the validated processed to sterilize and depyrogenate them are not located on site. This statement would apply to the paragraph starting on line 253 as the validated processes to sterilize and depyrogenate them are on site.
20	289-293	*"As part of the selection process, integrity testing of the drug product container closure system should be performed to verify its ability to maintain the quality of the finished drug product and sterility over the expiry period."* - Depending on the materials used in the construction of the container and closer chosen, freezing of containers can result in the sterility of the container being jeopardized. For this reason the text should include a requirement that the testing be performed using the storage conditions.
21	297-302	*"Procedures for storage if appropriate, of sterilized containers or closures must be established in a manner to minimize the risk of contamination and to maintain sterility (see § 211.80(a), 296 (b)). After storage for long periods or after exposure to air, heat, or other conditions that might adversely affect the drug product container, or closure, containers and closures must be re-tested or re-examined for identity, strength, quality, and purity (see § 211.87). However, the Agency does not intend to take action against an outsourcing facility regarding this additional testing if each lot of containers or closures is stored under the supplier's labeled storage conditions and protected from contamination when portions of the lot are removed."* As this is a single paragraph it reads as if it applies in its entirety to sterilized containers. If so: - The term "long periods" is too vague unless it is intended to relate to unopened packages of containers or closures that are within the expiration or retest date established. Containers or closures that are purchased sterile should be discarded after the supplier's expiration date. -If portions of an integral package are stored after opening, in addition to requiring that specific storage conditions be defined, a new expiration date should be established that ensures the sterility of the components are not compromised.
22	351	*"- The shipment's package integrity must be verified upon receipt before use."* - To ensure the proper verification of the supplier's packaging integrity a requirement that a formalized inspection process with specific instructions for each packaging configuration received should be required.

23	356-358	*"The quality of water produced on-site and used as a component or processing aid should be tested regularly at point of use to verify acceptable microbial quality and endotoxin limits."* – A requirement that the water system be validated should be included based on the criticality of water as a component as well as a processing aid.
24	360-361	*"Components must be re-tested or re-examined for identity, strength, quality, and purity after storage for long periods…."* – the term long periods needs to be replaced with a more definitive duration, e.g., periods exceeding the re-test date.
25	463	*"Introductory training on aseptic technique, cleanroom behavior, gowning, and procedures covering aseptic manufacturing area operations must be established and conducted before an individual is permitted to enter the aseptic manufacturing area or conduct operations in a laminar flow hood (see § 211.25(a))."* - To properly prepare the individual training should also include basic microbiology.
26	522-525	*"For sterile drug products that are filter sterilized, prefiltration bioburden and endotoxin limits should be established and measured prior to sterile filtration. A pharmaceutical sterilizing-grade filter should be used, and filter integrity testing should be conducted after each filtration or production run."* - Based on the criticality of this step a requirement should be added that the filtration process be validated.
27	526	*"For sterile drug products that are not subjected to overkill terminal sterilization, prefiltration bioburden limits should be established and measured prior to filtration."* - This appears to already be covered in the text in the paragraph above (Line 522-525).
28	602 and 679	*"…not to exceed 24 hours at USP controlled room temperature;"* - What is the scientific justification for this duration and temperature? This BUD (beyond use date) condition may allow for a greater than appropriate microbial risk.
29	606-608	*"If the batch size is very small and does not meet the criteria above for eliminating the sterility test when compounding pursuant to a prescription for a single patient, standard sterility tests may require that additional units be produced to be able to conduct the sterility test."* - Generation of additional units solely for the purpose of sterility testing may not add any additional valuable information beyond that derived from other controls or tests, e.g., media fills. The reference to USP<71> sampling plan may be inappropriate given the unique nature of compounding.
30	800	*"ISO 14644-1 "Cleanrooms and associated controlled environments – Part 1: Classification of air 800 cleanliness."* – should be 14644-1:1999