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October 28, 2003

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

Docket Number: 2003D-0382

Dear Sir or Madam:

The following comments are being submitted within the 60 Comment Period relative to the draft document issued on September 3, 2003, " Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing-Current Good Manufacturing Practice, dated August 2003".

Please refer to the submitted twenty-two (22) comments that include rationale and alternate text for your evaluation and use in the subject guidance document. See attachment .

Please contact me, Joe Lasich, for any questions or comments regarding the submitted comments.

Sincerely,

Joseph Lasich

Joseph Lasich
Senior Manager, Corporate Quality Technology
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2003D-0382

C7

Comments: FDA Draft Guidance (September 2003) Aseptic Processing/Sterile Products

J. Lasich DOCKET NUMBER: 2003D-0382

No	Section	Page	Line	Comment	Proposal 10/20/03
1	IV. Buildings and Facilities	4	133-137	Initial clean-room classification should not be derived from dynamic data.	**Rationale:** Clean-room qualification prior to routine production use should be performed under as-built and static conditions. Evaluation of the dynamic performance of the clean-rooms during routine production should be part of the environmental monitoring program. This provides more relevant data than a relatively short period of dynamic testing in the qualification phase. **Alternate Text:** Initial clean-room qualification should include some assessment of air quality under as-built and static conditions. The aseptic processing facility environmental monitoring program should also assess conformance with specified clean-room classifications under dynamic conditions.
2	IV. Buildings and Facilities	7	239-241	We interpret this to indicate that at least 12.5 pascals between rooms of the same classification is recommended.	**Rationale:** We agree with the prior sentence that a positive pressure differential of at least 12.5 pascals should be maintained at the interface between classified and unclassified areas. There is no need to maintain a pressure differential of at least 12.5 pascals between rooms of the same classification. A cascade pressure differential is important between the different classified areas. **Alternate Text:** A pressure differential should be maintained between the aseptic processing room and adjacent rooms(with doors closed).

No	Section	Page	Line	Comment	Proposal 10/20/03
3	IX.A.2, Validation of aseptic processing and sterilization. IX.A.9. Validation of aseptic processing and sterilization.	23 27	771-773 932-950	Repeat media runs should not be automatically required. A single run should suffice if the root cause is clear and corrections instituted. Revalidation indicates anywhere from one to three media fills depending on the investigation outcome.	**Rationale:** The number of runs should be based on the investigation outcome. **Alternate text:** For 771-773: If the outcome/cause is clear, narrow, not systemic in nature and the media history does not indicate contamination, one repeat media fill run is sufficient. Once corrections are instituted, the number of media fill(s) should be justified. For 950: Revalidation indicates a repeat of one to three media fills depending on the investigation outcome.
4	IX.A.7. Validation of aseptic processing and sterilization.	25	845-847	The guidance indicates an expectation for representative isolates from three areas (environmental monitoring, personnel monitoring and positive sterility tests) in addition to the USP organisms to qualify the media. It should not be necessary to use isolates from these three areas in addition to the USP organisms to qualify the media.	**Rationale:** The media selected should be qualified by USP testing requirements. **Alternate Text:** The media selected should be demonstrated to promote growth of USP <71> indicator microorganisms.

5	IX. Validation of aseptic processing and sterilization	22	727 and 732	Does this imply a fixed # of interventions and aseptic additions for routine production operations? We believe it is not necessary to simulate a discrete number of interventions.	**Rationale:** The actual number of interventions should not be simulated in a media fill. The number of typical interventions is proportional to the length of the aseptic filling operation. It is more important to simulate the type and complexity of the interventions in the media fill. **Alternate Text:** For 727: Type and complexity of normal interventions, atypical interventions, unexpected events(e.g. maintenance), stoppages, equipment adjustments and transfers. For 732: Aseptic additions (e.g. charging containers and closures as well as sterile ingredients).
6	V. Personnel Training, Qualification and Monitoring IX.C. Validation of aseptic processing and sterilization	14 29	439-443 1031-1032	As indicated sterile instruments ... might be interpreted to preclude use of decontaminated instruments. Does this indicate single use instruments that are sterilized via heat(for example) and not disinfected/decontaminated to achieve no viable bioburden? Does this indicate that bottle hoppers, dropper tips and closure tracks need to be sterilized?	**Rationale:** Both instruments and equipment surfaces used in clean rooms should always be sterilized or disinfected to render them contamination free. Sterilization processes (e.g. moist heat, dry heat, gamma sterilization and ethylene oxide) or disinfection processes using liquid or gaseous disinfectants **Alternate Text:** For 439: Instruments used in clean rooms should always be sterilized or disinfected to render them contamination free. For 1033: Equipment surfaces used in clean rooms should always be sterilized or disinfected to render them contamination free.

7	IV. Buildings and Facilities	6	214-215	This is inconsistent with the action level for ISO Class 5. This indicates any and all recovered contamination from air monitoring of critical areas(Grade A) should receive investigative attention.	**Rationale:** ISO Class 5 is not designed to be a sterile area. It is an aseptic area where a "low level" of contamination is expected. **Alternate Text:** Air monitoring of critical areas should have a target of no microbial contamination. Occasional microbial counts below the action level and not indicating adverse trends are acceptable.
8	Appendix 1, Aseptic processing isolators	48	1681-1684	Product should not be automatically rejected due to isolator breach.	**Rationale:** Product disposition should be dependent on the investigation outcome. A leak in an isolator does not automatically constitute a breach in product quality.The advantage of an isolator is the removal of all direct human interaction from the product and process. **Alternate Text:** Breaches of integrity should be investigated. If it is determined that the product has been compromised, appropriate action shall be taken.
9	IV. Buildings and Facilities	12	403-405	Limit scope of no drains to Class 100 and Class 10,000 areas only and not all classified areas.	**Rationale:** Properly designed drains are permitted in grades C and D areas There should be no drains in Grade A(Class 100) and B(Class10000) aseptic areas. **Alternate Text:** Drains are not considered appropriate for Class 100(ISO Class 5) and 10,000(ISO Class 7) areas. Properly designed drains are permitted in higher classification areas, such as Class 100,000, example: compounding.

10	IX.C.2Validation of aseptic processing and sterilization	31	1117-1118	It should be possible to accept the D value of the BI as determined by the supplier and stated on the C of A if handled and stored as indicated by the supplier.	**Rationale:** D value analysis may be accepted via certification as described in USP 26 if handled and stored as indicated by the manufacturer. **Alternate Text:** The biological indicator should be stored at the conditions indicated by the manufacturer and within the expiry date. The microbial count of the biological indicator should be confirmed before use. The D value may be accepted via manufacturers certification.
11	V. Personnel Training, Qualification and Monitoring	15	478-479	Delete Hair covering, shoe over covers and beard/moustache covers from elements of a sterile gown.	**Rationale:** These elements are donned prior to donning the sterile gown.Hair covering , shoe over covers and beard/moustache covers are not sterile and are worn under the sterile gown. **Alternate Text:** Gowns should be sterile and non shedding and should cover the skin and hair (face masks, hoods, protective goggles, elastic gloves, clean room boots are examples of common elements of gowns).

12	V Personnel Training, Qualification and Monitoring	15	491-494	Is Periodic re qualification maintained by routine monitoring or does it indicate a repeat of the initial qualification?	**Rationale:** Personnel re qualification can be attained with the use of monitoring data to re qualify personnel unless the monitoring data indicates a repeat of the initial qualification is warranted. **Alternate Text:** Following an initial assessment of gowning, representative locations on the gowns should be routinely tested as part of the monitoring program. If adverse trends are detected, the personnel should be requalified.
13	VIII. Time Limitations IX.B. Validation of aseptic processing and validation.	21 29	684-685 1019-1020	Sterilizing grade filters should generally be replaced following each lot. This may indicate that multiple use of sterilizing filters is not acceptable. Add provision for multiuse of sterilizing filters if validated.	**Rationale:** Multi-use sterilizing grade filters for the same product such as large volume liquid products is acceptable with proper validation. **Alternate Text:** For 684: Sterilizing-grade filters should generally be replaced following each manufactured lot. Multi-use sterilizing grade filters for the same product may be permitted if properly validated.

14	IX.B.Validation of aseptic processing and sterilization	28	985-987	determination of actual product bioburden(microorganism) size techniques not readily available and not routinely performed.	**Rationale:** Typically, bioburden testing of bulk product includes microbial count and does not include a determination of bioburden size. The use of a standard small size biological indicator challenge organism that covers the wide range of typical bioburden during sterile filter validation supports this approach. **Alternate Text:** A commercial lot's actual influent bioburden should not include microorganisms in a concentration that would present a challenge beyond that considered by the validation study.
15	IX.A.8., Validation of aseptic processing and sterilization	25	879-881	Add allowance for transfer after incubation into a clear container for visual inspection example: ointment tubes	**Rationale:** There are dosage forms, such as ointment tubes, that require transfer into a clear container for visual inspection. **Alternate Text:** For 881: For media fills that require containers that are not clear(e.g. metal or plastic ointment tubes) , the media is transferred into clear containers for visual inspection.

16	XII, Batch Record Review	44	1529-1530	This sentence should be clarified that a disruption in power supply may be important for the functioning of utilities such as HVAC and in such case can result in a manufacturing deviation.	**Rationale:** There may be power supply disruptions during aseptic production that do not adversely impact product quality. Each event needs to be investigated to evaluate impact on product quality prior to its determination as a manufacturing deviation. **Alternate Text:** Power supply interruptions during aseptic processing must be evaluated for impact on product quality. A manufacturing deviation report must be included in the batch records if product quality is affected.
17	V. Personnel Training, Qualification and Monitoring	14	437,439, 446,456, 459-460	The aseptic techniques noted are not possible to implement when applied to clinical lots that are manually filled and closed.	**Rationale:** Clinical materials of relatively small (less than 2000 units) lot sizes require manually intensive operations during filling and closing. Full duration media simulations validate the manual filling/closing operation. **Alternate Text:** For 437: Some of these techniques aimed at maintaining sterility of sterile items and surfaces for conventional semi-automated aseptic filling include: (They may not apply to manual aseptic filling operations).

18	IX.B. Validation of aseptic processing and sterilization	29	1020-1021	Integrity testing of filters before use can be performed prior to sterilization.	**Rationale :** Filter integrity testing should be performed when there is no contamination risk to the process or product. It is preferred to perform a pre-use integrity test on the assembled filter apparatus prior to sterilization. **Alternate Text:** Normally, integrity testing of the filter is performed prior to use after the filter apparatus has been assembled.
19	V. Personnel Training, Qualification and Monitoring	14	467	Refrain connotes an expectation of not talking. An operator should minimize not refrain from speaking in direct proximity to an aseptic processing line.	**Rationale :** In ISO Class 5 and ISO Class 7 aseptic filling rooms, personnel need to communicate at times to perform their duties in the direct proximity of an aseptic processing line. This common practice is qualified as part of the media fill program. **Alternate Text:** Also, an operator should minimize speaking when in direct proximity to an aseptic filling line.
20	IV. Buildings and Facilities	9	313	Revise approximately 25-100 mcg/L to approximately 20-100 mcg/L.	**Rationale:** Institute of Environmental Sciences, Testing Clean Rooms, indicates 20mcg/L is acceptable. Document #: #IES-RP_CC-006-84-T,section 5.1. **Alternate Text:** ...upstream of the filter in a concentration ranging from approximately 20 to 100 micrograms/liter....

21	VIII Time Limitations	21	675-676	Guidance indicates the period between the start of bulk product compounding and its filtration. This is limited in scope.	**Rationale:** There are other methods to sterilize a bulk product, example: moist heat. Replace its filtration with sterilization. **Alternate Text:** Time limits should include, for example, the period between the start of bulk product compounding and its sterilization, …
22	Appendix 1, Aseptic processing isolators	48	1710	Sterilization is used in lieu of decontamination	**Rationale:** To be consistent with line 1642. Replace sterilization with decontamination. **Alternate Text:** One should be aware that locations on gloves, sleeves, or half suits can be among the more difficult to reach places during surface decontamination.

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RECOMMENDED PRACTICE
Tentative

IES-RP-CC-006-84-T
November 1984

TESTING CLEAN ROOMS

Institute of Environmental Sciences
940 East Northwest Highway
Mount Prospect, Illinois 60056
312/255-1561

Recommended Practice No. IES-RP-CC-006-84-T is issued as a tentative document for use and comments. Comments and suggestions for changes and/or additions should be received by November 1, 1985 and should be addressed to: Institute of Environmental Sciences, 940 East Northwest Highway, Mount Prospect, IL 60056.

4.3.2 Calculate the arithmetic mean of all readings recorded in 4.3.1 and report as average airflow velocity in feet/min (m/sec).

4.3.3. Calculate the airflow uniformity range equal to the average airflow velocity, ± 20%.

4.3.4 Identify all readings which are outside the airflow uniformity range and calculate the percentage of readings which are within the airflow uniformity range

4.4 Acceptance

4.4.1 The maximum and minimum average velocities are a matter for agreement between Buyer and Seller.

4.4.2 The minimum percentage of airflow readings within the ± 20% uniformity range is a matter for agreement between Buyer and Seller.

5. HEPA FILTER INSTALLATION LEAK TEST

This test is performed to confirm that the HEPA filter system is properly installed by verifying the absence of bypass leakage in the installation and that the HEPA filters are free of defects and pinhole leaks. It is particularly important for laminar airflow and mixed airflow clean rooms where a Class 100 or better cleanliness specification is imposed.

The test is made by introducing an aerosol challenge upsream of the HEPA filters and scanning immediately downstream of the filters and support frame. This procedure detects small pinholes or other damage in the filter medium and frame seal, bypass leaks in the filter frame and gasket seal, and leaks in the filter bank framework.

Two different leak detection techniques are presented, along with recommendations for two different aerosol challenge methods and two different detection instruments. Appropriate tests are recommended for laminar airflow, mixed airflow, and turbulent airflow clean rooms.

5.1 Air-Generated Aerosol Challenge and Aerosol Photometer—Downstream Filter Scan Test Method

This method may be limited to small clean rooms where the specified aerosol challenge concentrations are achievable.

5.1.1 Apparatus

5.1.1.1 Air-Generated aerosol source per Par. 3.6.

5.1.1.2 Aerosol photometer with logarithmic or linear readout per Par. 3.8 and a sampling flow rate of 1.0 (±0.1) ft³/min. (.028 m³/min.). The probe inlet area should be 1.2 to 1.4 in² (7.8 to 9.2 cm²).

5.1.2 *Procedure*

This test is performed by introducing DOP or specified substitute upstream of the HEPA filters and searching for leaks by scanning the downstream side of the filters with the photometer probe. The design airflow velocity should be set prior to performing the filter installation leak test.

5.1.2.1 Introduce the aerosol into the air supplied to the HEPA filters in a manner which will produce a uniform challenge concentration at each of the HEPA filters being exposed at the same time.

5.1.2.1.1 Where construction permits, it is recommended that means be provided to challenge and test filters one at a time. Introduce the aerosol and measure the upstream concentration immediately upstream of the filter in question. Care must be exercised to assure uniform distribution of the challenge aerosol.

5.1.2.1.2 Where several, or all, filters must be exposed simultaneously to the aerosol, it is recommended that the aerosol be introduced at the blower inlet(s) or another location which will produce a uniform mixture over all filters. Measure the upstream concentration at a point immediately ahead of the filters under test.

5.1.2.1.3 Set the aerosol generator air supply pressure at 20 psig minimum. Operate one or more Laskin nozzles, and/or generators as necessary to produce the upstream concentration required for the leak detection photometer to be used.

5.1.2.2 Measure the upstream aerosol challenge concentration, using either a linear or logarithmic photometer scale.

5.1.2.2.1 For linear readout photometers (graduated 0-100), the upstream concentration should be established using one or more Laskin nozzles adjusted to read 10 to 20 micrograms of air on the upstream concentration. The photometer should be adjusted to read 100%.

5.1.2.2.2 For logarithmic readout photometers, the upstream concentration should be adjusted, using the instrument calibration curve, to give a concentration of 1.0×10^{1} above that concentration required to give a reading of one scale division.

5.1.2.3 The filter face and the perimeter of the filter pack should be scanned by passing the probe in slightly overlapping strokes so that the entire area of the filter is sampled. The probe should be held approximately 1 in (2.5 cm) from the area to be tested during scanning. Separate passes should be made around the entire periphery of the filter, along the bond between the filter pack and the frame, and around the seal between the filter and the device, at a traverse rate of not more than 10 ft/min (3 m/min).

Note: Prolonged exposure of filters to DOP should be avoided. SEE TEST DATA

5.1.3 Reporting

Report all leaks which exceed the following:

a) *For linear readout photometer:* a reading greater than 0.01% of the upstream challenge aerosol concentration.

b) *For logarithmic photometer:* a reading greater than one scale division.

5.1.4 Acceptance

5.1.4.1 HEPA filters may be repaired providing:

a) The size of the repair(s) is less than 5% of each filter face area, and

b) One dimension of any repair is limited to 1.5 in (3.8 cm) maximum, or as otherwise agreed upon by Buyer and Seller.

5.1.4.2 Repairs to filter installation leaks may be made by procedures acceptable to both Buyer and Seller.

5.2 Ambient Particle Aerosol Challenge and Airborne Particle Counter—Downstream Filter Scan Test Method

5.2.1 Apparatus

Optical particle counter having a minimum