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IN BUSINESS FOR LIFE

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

Subject: Docket No. 2003D-0382, Federal Register: September 5, 2003 (Volume 68, Number 172, Pages 52782-52783)

Genentech, Inc. appreciates the opportunity to comment on the Food and Drug Administration's (FDA's) draft Guidance for Industry: *Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*. Genentech, Inc. is a biotechnology company that has headquarters in South San Francisco, California.

Genentech, Inc. is very pleased with the work done to date on the draft guidance and believes that it will serve as a valuable resource for industry once implemented.

In the way of further enhancing the utility of the document, Genentech, Inc. offers the following commentary. For clarity, the comments and questions have been compiled into a single comment matrix (attachment).

If you have any questions regarding our comments, please contact Marc Baires, Regulatory Affairs Associate, at (650) 225-7959.

Sincerely,

Gene Murano, Ph.D.

Gene Murano.Ph.D.
Vice President, Regulatory Affairs,
Genentech, Inc.

2003D-0382 C27

Comment Matrix
Sterile Drug Products Produced by Aseptic Processing
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Line No.	Proposed Change/Clarification Request	Justification/Clarification Question
Lines 143-152	Please remove from Table 1-Air Classifications, the microbiological Settling Plates Action Levels and footnote d, "~~The additional use of settling plates is optional.~~"	Action levels for optional methods should be established based on process requirements and environmental monitoring.
Line 196	Please replace the word 'laminar' with the word unidirectional in the following sentence. "Air in critical areas should be supplied at the point of use as HEPA-filtered ~~laminar~~ unidirectional flow air . . ."	For consistency within this section, use the word unidirectional versus laminar.
Line 200	Please remove 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 setpoint. Higher velocities may be appropriate in operations generating high levels of particulates	There is no scientific basis for recommended air velocity. Velocity should be established based on process requirements and environmental monitoring.
Line 215	Please replace the term 'contamination' with 'recovery' in the following sentence. "Air monitoring of critical areas should normally yield no microbiological contaminants. ~~Contamination~~ Recovery in this environment should receive investigative attention"	The use of the word contamination here implies a conclusion prior to performing an investigation.

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Line No.	Proposed Change/Clarification Request	Justification/Clarification Question
Lines 238-239	Delete example of acceptable positive pressure differential pressure. " ~~For example, a positive pressure differential of at least 12.5 Pascals (Pa) should be maintained at the interface between classified and unclassified areas.~~"	There is no scientific basis for having12.5 Pascals as a target for maintaining positive pressure differential. Differential pressure should be established based on process equipment and environmental monitoring.
Line 241-242	Please delete the comment regarding the strict control of doors. "When doors are open outward airflow should be sufficient to minimize ingress of contamination. ~~, and the time that a door can remain ajar should be strictly controlled.~~"	Since airflow should be sufficient to minimize ingress of contamination, the placement of controls on the time a door can remain ajar is redundant. Doors should only be strictly controlled where they are a feature of a facilities environmental control.
Line 247 – 249	Please remove requirement of 20 air changes for Class 100,000 (ISO 8) supporting rooms. "~~For Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve at least 20 air changes per hour would be typically acceptable.~~"	Lower amount of air changes should be acceptable if they maintain appropriate level of air quality and should be established based on process requirements and environmental control.
Line 262 – 264	Please make the following clarification correction. "A compressed gas should be of appropriate purity (e.g., free from oil and water vapor) and its microbiological and particle quality should be ~~equal to or better than air in the environment into which the gas is introduced~~ appropriate for its use.	For clarification.

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Line 292	Please clarify that HEPA filters in the hot area of a depyrogenation oven or tunnel may be tested using particle counts.	These filters cannot be integrity challenge tested at high temperatures and results at ambient temp may not be representative of use conditions.
Line 311 – 314	Please replace the term 'DOP' with 'aerosol' in the following sentence. "For example, depending on the accuracy of the photometer, a(n) ~~DOP~~ aerosol challenge should introduce. . .:	In lines 297 and 298, both Dioctylphthalate (DOP) and Poly-alfa-Olefin(POA) are given as examples of appropriate leak testing aerosols. Therefore, the generic term aerosol is more appropriate here.
Line 311 – 314	Please remove the suggested aerosol concentration target range. "For example, depending on the accuracy of the photometer, (*an aerosol*) challenge should introduce the aerosol upstream of the filter in a concentration ~~ranging from approximately 25 to 100 micrograms/liter of air at the filter's designed airflow rating.~~ whereby a leak may be detected by the detection system."	Any range in which a leak may be detected should be appropriate.
Line 317 – 318	Please add the comment 'at an appropriate rate' to the end of the sentence. "Scanning should be conducted on the entire filter face and frame at a position about on to two inches from the face of the filter *at an appropriate rate*."	For clarification

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Line 326	Please add the comment 'for critical areas' to the beginning of the following sentence. "*For critical areas,* this testing is usually done on a semi-annual basis."	For clarification.
Line 327-328	Please add the suggested comment after the words 'adjacent filters. "It is important to conduct periodic monitoring of filter attributes such as uniformity of velocity across the filter (and relative to adjacent filters) to *confirm consistency with established baselines. If variations in filter to filter velocity are present, such conditions should be justified by airflow studies."*	Based on physical properties of equipment and room it may be necessary to adjust individual filter velocities to achieve optimal unidirectional airflow.
	Please replace "generally" with "may" and also replace "contamination" with "turbulence" in the following statement. "Variations in velocity ~~generally~~ may increase the possibility of ~~contamination~~ turbulence, as these changes (e.g., velocity reduction) can have an effect on unidirectional flow.	The wording implies conclusions prior to performing an investigation. Each case is likely to have unique factors that should be considered.
Lines 392-393	Please replace the word 'disinfected' with 'sanitized' in the following sentence. "In this regard, materials should be ~~disinfected~~ sanitized in accord with appropriate procedures."	Guidelines for acceptable limits are established for sanitized materials.

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Lines 403-405	Please replace word 'classified' with 'critical' in the following sentence. "With rare exceptions, drains are not considered appropriate for ~~classified~~ critical areas of the aseptic processing facility."	For clarification.
Lines 433-435	Please respond to the question (see right) regarding the following statement: "Similarly, the quality control unit should provide regular oversight of adherence to established, written procedures and basic aseptic techniques during manufacturing operations."	Would this require additional documentation of routine evaluation beyond that provided by supervisors or quality oversight?
Lines 493-494	Please define the term "automated operations" in the following statement: "Semi-annual or yearly re-qualification is sufficient for automated operations where personnel involvement is minimized."	Please define "automated operations" and provide examples.
Line 595-598	Add the phrasing "or worst case loading pattern" to the sentence "Validation of dry heat sterilization and depyrogenation should include appropriate heat distribution and penetration studies as well as the use of worst case process cycles, container characteristics (e.g., mass), and specific loading configurations to represent actual production runs *or worst case loading patterns*"	Specific loading configurations are not applicable to depyrogentation tunnels.

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Line 732	Please add the word 'representative' to the beginning of the bullet point. "*representative* number of aseptic additions. (e.g., charging containers and closures as well as sterile ingredients)	For clarification
Line 761	There should be a paragraph break in line 761. " . . . consistent with the nature of each operator's duties during routine production. Each change to a product or line change . . . :"	Grammatical correction.
Line 823-825	Please edit the following sentence as shown. "~~Each individual~~ (M)edia fill(s) ~~run~~ should evaluate ~~a single worst-case~~ line speed, and the speed chosen for each run during a study should be justified"	Media fills should challenge line speeds at high and low speeds.
Lines 865-866	"Media units should be incubated under conditions adequate to detect ~~organisms that can otherwise be difficult to culture~~ a wide range of organisms."	The statement currently implies that it is possible to detect cultures that cannot be cultured under the specified operating conditions.

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Line No.	Proposed Change/Clarification Request	Justification/Clarification Question
Line 869-875	Remove requirement that temperature should be maintained within 2.5°C of the target temperature. "Incubation temperature should be suitable for recovery of bioburden and environmental isolates and should at no time be outside the range of 20-35°C. ~~Incubation temperature should be maintained within 2.5°C of the target temperature. If two different temperatures are used, the total incubation should not be less than 14 days~~" Incubation time should not be less than 14 days. ~~If two temperatures are used for incubation of the media filled samples the samples should be incubated for at least 7 days at each temperature.~~"	A temperature range of 20-35°C is already established as adequate for incubation.
Line 920-921	Add phrase 'if possible" to beginning of sentence. "*If possible*, the microorganisms should be identified to species level."	It is not always possible to identify to the species level.

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Lines 927 – 944	The bullet point examples in lines 935-944 should be modified to align with text in lines 927-930. "The number of contaminated units should not be expected to increase in a directly proportional manner with the number of vials in the media fill run. Test results should reliably and reproducibly show that the units produced by an aseptic processing operation are sterile. Modern aseptic processing . . . • ~~When filling fewer than 5000 units, no contaminated units should be detected.~~ • ~~When filling from 5, 000 to 10, 000 units:~~ -- 1 contaminated unit should result in an investigation including consideration of a repeat media fill. -- 2 contaminated units are considered cause for revalidation, following investigation. • ~~When filling more than 10, 000 units:~~ ~~-- 1 contaminated unit should result in an investigation including consideration of a repeat media fill.~~ ~~-- 2 contaminated units are considered cause for revalidation, following investigation.~~	No contaminations should be observed, regardless of the number of units filled. The course of action prescribed by the guidance for one and multiple contaminations are applicable to all fill sizes.

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Lines 1050-1052	Please delete the following sentence. "For both the validation studies and routine production, use of a specified load configuration should be documented in the batch records."	Specified loading patters should not be required where validation can demonstrate that worst-case loading patterns do not impact the validated system.
Lines 1099-1100	Please replace the word locations with the word item(s). "Ultimately, cycle specifications for such sterilization methods are based on the delivery of adequate thermal input to the slowest to heat ~~locations~~ item(s)"	For clarification.
Lines 1114-1115	Please split the bullet point in lines 1114 and 1115 into two separate bullet points as follows. • *Calibrate system monitors at suitable intervals.* • *Calibrate devices used for validation before and after validations runs.*	System monitors should not need to be calibrated before and after validation runs.
Lines 1306-1307	Please replace the term ' is generally' with the term 'can be' in the following sentence. "Total combined yeast and mold count ~~is generally~~ can be obtained by incubating at 20 to 25°C for 5 to 7 days."	The term 'is generally' in this statement implies that yeast and mold is not consistently obtained by incubating under the specified conditions.
Lines 1346-1347	Please define the term 'closing operations' in the following statement. "The testing laboratory environment should employ facilities and controls comparable to those used for filling and closing operations."	Please define and/or provide examples of "closing operations."

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Line 1411	Please delete the current sentence in line 1411 and replace with the verbiage from footnote 12, describing when an initial positive sterility test is invalid. "~~It is difficult to support invalidation of a positive sterility test.~~ A positive sterility test is invalid, if and only if microbial growth can be without a doubt ascribed to laboratory error. (Reference USP)	For clarification.
Lines 1547-1548	Please replace the word 'can' with the word 'may' in the following sentence. "However, a leak in any of certain components of the system ~~can~~ may constitute a significant breach of integrity."	Grammatical clarification.
Line 1556	Please define the term 'critical breach' in the following sentence. "A faulty glove or sleeve (gauntlet) assembly represents a route of contamination and a critical breach of isolator integrity."	Please clarify the term "critical breach" since not all breaches are critical depending on size, location, and depth.
Line 1562	Please replace the word 'can' with the word 'may' in the following sentence. "Such a breach ~~can~~ may be of serious consequence."	Grammatical clarification.

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Lines 1564-1566	Please answer the question (see right) regarding the following statement: "Due to the potential for microbial migration through microscopic holes in gloves and the lack of a highly sensitive glove integrity test, the inner part of the installed glove should be sanitized regularly and the operator should also wear a second pair of thin gloves"	Is it acceptable to place sterile gloves over the isolator gloves?
Lines 1770-1772	Please define the term 'boiling system' in the following sentence. For example, because of its potential to contaminate the sterile drug product, the integrity of the cooling or boiling system (e.g. mold plates, gaskets) should be carefully monitored and maintained.	Please define the term "boiling system". Does this include any heating system?