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Janet Woodcock, MD
C/O Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Ref: Docket No. 2003D-0382

Dear Dr. Woodcock:

We are pleased to have the opportunity to review and comment on FDA's Draft Guidance for Industry on *"Sterile Drug Products Produced by Aseptic Processing"*. We believe our comments might serve to increase the utility of this guidance and to minimize any potential for misinterpretation or misunderstanding.

It should be noted that these Johnson & Johnson comments encompass those of several of it's operating companies including ALZA Corporation, Centocor Inc., Janssen-Cilag International, Ortho Biotech Products L.P., and Ortho-McNeil Pharmaceutical, Inc.

Sincerely,

Rainer Newman

Rainer F. Newman
Director Pharmaceutical Science

cc: Mr. L. Fantasia
Mr. D. Liu
Dr. R. Morrissey

2003D-0382

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Line(s)	Comment	Recommendation
111-112	The statement might suggest to some readers that aseptic processing is not an acceptable precursor to terminal sterilization. Clearly it is.	*"It is a well-accepted principle that sterile drugs should be terminally sterilized, and that only if terminal sterilization is not feasible should aseptic processing be the alternative".*
114-115	***"In such cases a manufacturer can explore the option of adding adjunct processing steps..."*** *Adjunct processing* is neither defined nor further discussed within this guidance.	This guidance should not introduce new topics outside of aseptic processing.
125	"***aseptic processing facilities must have separate areas of operation..."*** This implies that only unique facilities would be acceptable, while 21CFR211.42 states "...separate *or defined areas...*"	"*aseptic processing facilities must have* ***separated*** *areas of operation..."*
131-137	"...***the final room or area classification should be derived from data generated under dynamic conditions***.." Performance under dynamic conditions is clearly important, but this section implies that an area is classified by its performance rather than by its intended use.	Classifications should be based on, and meet, the level of their intended use. A filling line, for example, would not be acceptable if it's performance based classification were Class 100,000.
152 & 932	***"e – Samples from Class 100 (ISO 5) environments should normally yield no microbiological contamination"*** This statement is inconsistent with the current concept of good environmental bioburden control because it implies that a non-zero result is unacceptable. While an extremely low environmental bioburden should be the target, this statement might set unreasonable expectations.	One alternative is the EU Annex 1 approach, i.e., requiring an **average** of less than 1 CFU from all samples. Another might be to give examples of what action should be taken, for example *"the action should include a review of environmental monitoring trending data".*
183	The term ***"shift"*** does not have a universal or uniform definition and therefore its use will lead to confusion and disagreement.	Industry generally considers a shift as a time and people contiguous operation. For purposes of this guideline, we suggest that a shift is any continuous operation where essentially the same people are involved.

Line(s)	Comment	Recommendation
196	***"Air in critical areas should be supplied at point of use as HEPA-filtered laminar flow air at a velocity sufficient to sweep particles away...."*** "at point of use" might be both unnecessarily restrictive and unclear. "laminar flow" is largely theoretical and typically not achievable in real situations.	*"Critical area air is supplied via HEPA filtration at a velocity and with uni-directional flow sufficient to sweep particles from the critical area"*
202	***"Proper design...turbulence...stagnant air...eddy currents"*** Turbulence, stagnation and eddy currents are in themselves not the issue. The intent should be to insure that contamination is prevented from being introduced or accumulated in the critical zone.	Re-word this section to identify the intended result rather than possible causes of such a result. This is accomplished by the subsequent sentence , i.e, *"Air pattern analysis..."*
213	This line has the same problem identified in line 152, and contradicts, or is inconsistent with, line 149 note c.	See suggestion for line 152
238	***"...a positive air pressure of at least 12.5 Pascals..."*** There is no technical basis for such specificity. In some instances this pressure differential may be sufficient, too much or too little.	Delete the numerical differential and rely on the requirement for positive or over-pressure between areas of differing criticality.
243	***"Pressure differentials between cleanrooms should be monitored continuously... and frequently recorded..."*** The requirement is overly prescriptive. Validated and alarmed systems obviate the need for frequent and thus voluminous, recording of "good" data. Further, there is no practical value in pressure differentials between areas of the same classification, as this sentence implies. While there may be design situations requiring cascading pressures within a classification, pressure differentials should only be required between areas of differing classifications.	*"Pressure differentials between areas of differing classifications should continuously or frequently be monitored and deviations from acceptable differentials should be alarmed, and these alarms should be recorded"*
249	***"For areas of higher air cleanliness, significantly higher air change rates will provide...."*** Air change rate is not a measure of quality. In some cases, higher air change rates may lead to turbulence, and thus lower quality.	*"The air change rate should be sufficient to provide the level of cleanliness required in each operating area."*

Line(s)	Comment	Recommendation
272	***"Sterilized holding tanks and any contained liquids should be held under continuous overpressure..."*** Although overpressure is a frequent approach, it is not practical in all instances. Some containers may not be suitable for overpressurization.	*"Sterilized holding tanks and other containers holding sterile liquids should be over-pressured with a sterile gas or sealed in such a manner as to prevent contamination."*
312	***...a DOP challenge should be introduced..."*** Specifying DOP limits the opportunity for alternative, and safer materials. (Note: DOP (dioctylpthalate) is a suspected carcinogen)	*"...an appropriate aerosol challenge..."*
327	***"It is important to conduct periodic monitoring..."*** This wording is vague and should be deleted or replaced with current practice, which is semi-annual monitoring.	*"It is important to conduct semi-annual monitoring..."*
331	***""... and at defined distance proximal to the work surface..."*** Air velocity near the filter face is an indirect indicator of filter function. But air velocity near the work area has no practical value. By design the air sweeps over and away from the work area which means that not only differing velocity but also differing directions will be encountered. The validation, in particular the smoke study, is typically the appropriate determinant of appropriate air movement at work surfaces, not an arbitrary velocity profile.	Eliminate the wording on air velocity near the work surface.
373	***"Facility design should insure that the area between a filling line and the lyophilizer....provide Class 100 protection"*** This does not allow for alternatives that are often employed, i.e., transport via sealed, sanitized or sterilized containers.	*"Transport of partially closed product should only be in a critical (Class 100) area or via sealed containers."*
404	***"... drains are not considered appropriate for classified areas of aseptic processing facility."*** Drains are required in classified areas, e.g., Class 100,000 stopper preparation areas.	*"...drains are not considered appropriate for Class 100 areas..."*
535-540	This section requires that each component of the pre-sterilized product be evaluated for bioburden, presumably on a regular or per batch basis. Components of products should be evaluated for bioburden based on their source (e.g., biological material) and their likelihood of being contaminated.	It should be indicated that component bioburden testing is not a routine requirement.

Line(s)	Comment	Recommendation
612	***"The time between washing, drying (where appropriate), and sterilizing should be minimized...."*** The practice of purchasing pre-washed and dried stoppers is not recognized by this statement. In that case, the time between drying and sterilization may be substantial. Validation should be the means to address this issue.	*"The time between washing, drying, and sterilizing should be **validated**...."*
624	***"The finished dosage form manufacturer is responsible for the review and approval of the contractor's validation protocol and final validation report."*** While manufacturers should review contractor validations related to their products, they should not approve them. The conduct of validations at contractor locations, should be the responsibility of the contractor. A contractor validation may be applicable to more than one customer's product(s).	*"The finished dosage form manufacturer is responsible for the review of the contractor's validation protocol and final validation report*
629	"A container closure system that permits penetration of air..." All containers have an air and water vapor transmission rate, albeit many being extremely low.	Eliminate the word "air"
660	"Endotoxin control should be exercised..." If it is the intention of this sentence to suggest that proper cleaning is a means of endotoxin control, then the prior sentence is sufficient. If it is intended to mean something else, then it is unclear as to what. It is not common practice to routinely monitor surfaces for endotoxins, either before or after a sterile filtration.	Delete sentence
666	***"Equipment should be dried following cleaning."***	*"Equipment should be dried following cleaning, except when that equipment is to be promptly sterilized."*
722	***"Media fill studies should simulate aseptic manufacturing operations as closely as possible, incorporating a worst-case approach."*** Worst-case has little meaning since we can always imagine a case worse than the previous one. Planned as well as known, but unplanned, interventions should be simulated.	*"Media fill studies should simulate aseptic manufacturing as closely as possible, incorporating all functions and interventions such as:..."*

Line(s)	Comment	Recommendation
739	***"Operator Fatigue"*** It seems both unsafe and unreasonable to include operator fatigue in a media fill. Operator fatigue is more appropriately addressed in each organization's safety and work rules.	Delete bullet
771	***"Once corrections are instituted, repeat process simulation runs...."*** This requires and unspecified number of runs. Often one follow up run is sufficient.	*"Once corrections are instituted,* ***a repeat simulation run****..."*
780-786	This section implies that the duration of a routine aseptic operation determines the media fill size. This is inconsistent with other guidance, even within this draft.	The number of media fill units should insure that all functions and interventions are included, and should be large enough to achieve a desired confidence level in the specified result criteria.
822	***"The media fill program should adequately address the range of line speeds (e.g., by bracketing all vial sizes and fill volumes..."*** Confusing. Line speeds are not bracketed by vial sizes or fill volumes, although these should be incorporated into a bracketing design.	Clarify
877-878	***"Each media-filled unit should be examined for contamination by personnel with appropriate education, training and experience in microbiological techniques"*** This sentence appears to require a microbiologist to "read" media fills. That is both onerous and unnecessary.	*"Each media-filled unit should be examined by personnel who are trained to detect contamination."*
Footnote 9	Incubating units from setup operations which would never become part of the production run should not be required or recommended.	Delete footnote
937-944	The guidance for media fills greater than 10,000 units is the same as the guidance for runs of 5,000-10,000 units. While it is clear that the target for any media fill is no contaminated units, there must be a science based approach that recognizes that a larger number of units will increase the likelihood of a false or a real positive.	The guidance on run sizes and numbers of positives should reflect a statistical approach, i.e., to achieve a required confidence in an acceptable rate.

Line(s)	Comment	Recommendation
967-969	***"...reproducibly removes all microorganisms from the process stream..."*** While in practice this is the normal result, the sentence is technically incorrect. Sterilizing filters are validated to remove a specified concentration of a specified microorganism from a fluid stream. As such it reproducibly removes bacteria, yeasts and molds of approximately 0.2 mircometers diameter and larger	Reword or delete.
1009	***"The specific type of filter used in commercial production should be evaluated..."*** Commercial filter units are not typically evaluated in retention studies, but the specific type of filter material (membrane) is.	*"The specific type of filter* ***membrane****..."*
1050	***"For both the validation studies and routine production, use of a specified load configuration should be documented in the batch records."*** This sentence does not recognize the acceptable practice of bracketing minimum and maximum load configurations to qualify a cycle.	*"For both the validation studies and routine production, the load configuration should be documented in the batch records."*
1073	***"...consider the age of the sterilizer..."*** Revalidation is a time or event (performance) based activity that is independent of equipment age.	*"The formal program providing for regular revalidation should consider the sterilizer past performance."*
1117	***"The microbial count and D-value..."*** Accurate D-value determinations involve many variables and require specialized techniques, experience and equipment (e.g., BIER vessels). BI suppliers (who have expertise in this determination) are better able to accurately determine D-values which, as a result, should be accepted on certification.	*"The microbial count of a biological indicator should be confirmed before a validation study. The biological indicator D-value is established and certified by a qualified supplier"*
1153 & 1248	***"For example product contact surfaces, floors, walls, ceilings, and equipment..."*** Ceilings and floors should not be part of the routine monitoring program except perhaps during area validation and investigations.	Delete the word "floors...ceilings"

Line(s)	Comment	Recommendation
1178	***"Because of the likelihood of false negatives,..."*** Failing to detect an organism because its location was not sampled, is not the same as a false negative. This section gives no weight to false-positives, which are more likely to occur.	*"Because of the potential for not always detecting low levels of environmental bioburden..."*
1233	***"Therefore a sound disinfectant program includes a sporicidal agent, used according to a written schedule..."*** Sporicidal agents should be used sparingly when environmental monitoring results indicated their need.	*"Therefore a sound disinfectant program includes a sporicidal agent, used* ***as indicated by the environmental data****..."*
1297 – 1298	***"Rapid genotypic methods..."*** This guidance should not detail methods of identification. Each method has advantages and drawbacks. Emphasis should be on uniform methods in order to have value in comparing one isolate to another.	Delete sentence
1390	***"...it is important that an appropriate number of units are tested."*** This guidance suggests something other than USP methods should apply. (Note: there should not be a discussion of sterility testing in a aseptic processing guidance)	Delete sentence.
1549	***"The integrity of gloves, half-suits, seams, gaskets and seals should receive daily attention..."*** Requiring daily attention to these items individually is neither practical nor necessary. Pressure decay, pressure hold, or similarly encompassing evaluations should be done before each operation.	"The integrity of gloves, half-suits, seams, gaskets and seals should receive **routine** attention."
1581	***"In most sound designs, air showers over the critical zone once, and then is systematically exhausted."*** This is not correct. In many sound system designs, the air is recirculated (through HEPA filters), not exhausted.	Delete sentence
1588	***"...ease of cleaning and sterilization..."*** Isolator components are designed to be decontaminated but are not sterilized.	"...ease of cleaning and decontamination..."

Line(s)	Comment	Recommendation
1611	***"The interior of the isolator should, at minimum, meet Class 100..."*** Since there is no classification higher than Class 100 specified in this document, the phrase "at minimum" should not be included, as it implies that higher classes have been defined.	Delete "...*at minimum*..."
1615	***"An aseptic processing isolator should not be located in an unclassified room."*** Unnecessarily restrictive. Since there is no classification greater than Class100,000, it is tantamount to specifying that classification. Provided the process is validated, isolators can be located in any controlled environment.	*"An aseptic processing isolator should not be located in an* ***uncontrolled*** *room."*
1620	***"The ability to maintain integrity and sterility of an isolator..."*** As noted in other sections, the interior of isolators are not normally *sterilized*, but decontaminated.	*"The ability to maintain integrity and* ***low bioburden*** *of an isolator..."*
1639	***"Sufficient overpressure should be supplied and monitored on a continuous basis at this location (the mousehole)..."*** Pressure in a container, whether leaking or not, is everywhere the same. The monitoring of pressure would be the same regardless of location.	*"Sufficient overpressure should be supplied and monitored on a continuous basis to insure that isolation is maintained."*
1648	***"For example, to facilitate contact with the steriliant..."*** Sterility and decontamination are misused in the section on isolators. As noted above, isolator interiors are not sterilized as a routine, but decontaminated.	*"For example, to facilitate contact with the* ***decontaminant****..."*
1654	***"...free of viable microorganisms."*** Same comment as for line 1648	
1912	Relevant guidance documents are listed by title only	Include revision or date of document.