September 26, 2003

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

Ref: Docket No. 2003D-0382

Dear Sir or Madam,

Enclosed are comments to the "*Draft Guidance - Guidance for Industry Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice***"**.

I found the draft guidance deficient in many areas. While an update to the prior 1987 guidance may have been deemed required by many in industry and FDA, this effort is deficient in a number of ways:

- That aseptic processing environments must be 'sterile' as highlighted by repetitive statements requiring that facilities "… normally yield no microbiological contaminants". (Line 214). Given that personnel are present in manned cleanrooms and perform all of the activities including microbial sampling such a perspective is unrealistic. Moreover the document addresses "false negatives" in sampling, yet fails to consider the possibility of "false positives". (Lines 1174 & 1178).
- The document doesn't harmonize with either EU Annex 1 or the ISO 14644 series. FDA requirements are different numerically; require dynamic classification; obviate averaging of results (required in the EU Annex 1).
- The guidance document apparently believes that environmental monitoring of aseptic environments is a truly quantitative activity, when it is widely recognized that such a premise is clearly invalid scientifically. Precise measurement of low numbers of microorganisms whether in air or surface samples is a virtual impossibility, yet this guidance consistently requires both precision and accuracy that is not available with any present day sampling system or method.
- Appendix 1 of the guidance addresses isolation technology yet leaves the clear impression that this technology is less capable than manned cleanrooms. There are several statements made in this appendix raising the suspicion of a problem with isolators, where cleanroom practices are even less secure (Lines 1546-1552, 1556-1566, 1604-1605, 1656). If FDA's goal is to improve the safety of aseptically produced products then its treatment of isolators should be supportive of the technology. Isolators have been clearly demonstrated to be superior in all respects to aseptic processing in manned cleanrooms. To impede their further adoption as has certainly been the case in the United States relative to both Europe and Japan is inappropriate and risky to the public health. Isolators do not

PO Box 899, Belle Mead, NJ 08502-0899 [908] 874-7558 FAX [908] 874-8161
JAgalloco@aol.com

have to be perfect to aseptically produce sterile products with greater confidence than is attainable in any manned environment.

- The document contains far too many speculative opinions that are unsupportable scientifically. To venture that far from sound scientific principles reduces the guidance's effectiveness. Where guidance is given that is not based on scientific fact, firms are essentially forced to implement practices inconsistent with the physical laws of nature, an unfortunate and often expensive practice. In a few cases, the guidance draws on older (and obsolete) references to maintain outdated perspectives inconsistent with what are now well established facts.
- The document includes brief coverage of subjects better addressed elsewhere, e.g., sterilization, sterility testing, facility / isolator design. These subjects have been more fully addressed elsewhere (sterilization, sterility testing) or are so new in concept (isolator technology) that the guidance provided is either deficient, incorrect, and/or misleading. As these subjects are somewhat peripheral to the key subject, they should be mentioned in passing or not at all. Their inclusion in the guidance can certainly be stifling of innovation.
- The document is inconsistent with FDA's announced CGMP initiative "Pharmaceutical CGMPs for the 21st Century: A Risk Based Approach". The non-scientific nature of the guidance inhibits innovation, process improvement and raises unnecessary compliance concerns in areas with no impact on product safety. The number of unrealistic cautionary statements made regarding isolators will undoubtedly slow the implementation of this superior technology that has the potential to replace the more risky manned cleanroom.

My difficulties with this document are so extensive, that I encourage FDA to consider another draft of this guidance before issuing its final version. I think it unlikely that all of the necessary changes required to make this document usable across the industry can be made successfully in a single step. I trust that these comments will prove useful to FDA as it works to improve this guidance prior to finalization.

Sincerely,

James Agalloco
Agalloco & Associates

Line #	**Comments**
81	The footnote at the bottom of this page adds little to the document. That aseptic processing begins at different points in different processes is well recognized. Delete the footnote.
83	Delete the word "extremely". It adds nothing to the sentence. If the sentence must be modified perhaps using Class 100 (EU Grade A) in place of "extremely high-quality" makes the document definitive rather than subjective.
86	Replace "sterilization" with "depyrogenation" which is the more relevant process to aseptic filling of glass containers.
88	Delete "also", it adds nothing to the sentence
104	Change to read "… upstream aseptic bulk processing." The coverage of sterile bulk is not a part of this document, nor should it be. Non-aseptic bulk processing is wholly outside the scope of this document.
114	Delete the last sentence in this paragraph. It is wholly out of scope within the context of aseptic processing. While there is potential merit to the treatment, a major "requirement" should not be inserted into this document without careful consideration of the implications. FDA could not get its 1991 CGMP revisions regarding the preference for terminal sterilization into the regulation, and it should not 'back door' that in an aseptic processing guidance. Address it properly elsewhere, but don't do it here.
118	The footnote is trite, that anything else should be the case is absurd.
133-136	Classification of clean rooms is performed under static conditions, the individuals / firms who design them have no means to project the operating practices of the firm. They often design there rooms well in excess of the minimal classification requirements to allow for contributions from operations. Change the sentence to read "*Initial clean room classification should include an assessment of air quality under static conditions, the room should operate within the expected limits under dynamic conditions (i.e., with personnel present, equipment in place, and operations ongoing).*" Classification of environments is always done under static conditions and does not consider the microbial profile of the environment.
142	Change the title to read "Monitoring Expectations for Aseptic Processing Areas". As noted before dynamic classification is not commonplace and imposes requirements at the time of classification that are unworkable. The table includes FDA's expectations for environments under dynamic conditions and nothing more, ISO 14664-1 does not include microbial limits, as these relate to the practices of the facility owner and have virtually nothing to do with the classification. Additionally the table should be restricted to application for aseptic processing as classified environments are often used where strict microbial control is not required. Firms will often use classified environments for other reasons

	(i.e., particle control, cross-contamination prevention, environmental safety, etc.) and therefore there should be no expectation that a particular particle classification implies a particular microbial count. This is even true where Class 100 hoods are used in preparations areas, where no aseptic processing ever takes place. As constructed this table is overly restrictive as it implies that all classified environments of the same class must meet the same microbial limit. The use of Class 1,000 is uncommon and there is no reason to include it in the table. The values for microbial counts should be harmonized with EU Annex 1. Firms should not be held to different standards.
146	Note A should be deleted. Rooms cannot be classified under dynamic conditions by the designer / fabricator / contractor.
152	This is linked to later statements regarding these environments where "false negatives" are cited as a concern. There must be recognition on the part of FDA that "false positives" are perhaps equally likely. To expect that the sampling of a critical surface is anything other than a potentially contaminating intervention at that location is naï ve. There is no reason to expect that only operating interventions cause contamination, and that sampling interventions cannot! Either delete the footnote or revise it to read " The goal for samples from Class 100 (ISO 5) environments is zero, however occasional low level microbial counts may be encountered."
169	The presence of large numbers of very small particles (remembering that particle counts count different sizes independently, should also mean that in the absence of larger particles (>5 um) there is perhaps no linkage at all between particle and microbial counts. Moreover, the recent studies where such a linkage has been explored have been performed in unclassified environments of substantial count. The implications for that data are irrelevant to the tightly controlled environments found in the pharmaceutical industry. While particle control is important, that importance is generally relative to the deleterious effect of the particles themselves and not their potential as 'carriers' of microorganisms.
187-194	The potential for product aerosols goes beyond powder filling, it has been encountered with ointments and aqueous products as well. If a firm has clear evidence that the product is the source of the particles, then the approach listed in the paragraph should be applicable. Delete the word "powder" which appears four times in this paragraph to generalize the concept.
198-200	The footnote at the bottom of the page speaks to a definitive value for velocity within a Class 100 (ISO 5) environment. The choice of a reference from 1972 speaks volumes here because no contemporary cleanroom document would include such an outdated perspective. FS

	209C published in November 1987 eliminated velocity as a requirement, and its continued presence in standards anywhere is absurd. There is absolutely no scientific evidence to support its continued presence in this or any other standard. Delete both the reference and the footnote, the sentence works perfectly well without either, and allows flexibility in design and operation that their continued presence doesn't allow. Aseptic processing Isolators for example have been successfully operated at substantially lower velocities. The firm must always have control over its systems and specifying a specific velocity doesn't alter that as a requirement.
205-207	Air studies are interpreted subjectively, and while the general sense of what is written here is acceptable it must be clear that these studies can be cannot be interpreted to rigidly.
207-208	If by well documented, you mean videotaped, then this is acceptable, however, few would interpret a video of a smoke study as documentation in the strict sense. Why not explicitly require videotaping with a brief summary of conclusions? Forcing a written conclusion on visual observation of a smoke study is folly.
211-212	This sentence offers nothing in the way of benefit to the reader. Poor practices are poor practices, and it's not clear what the sentence requires in the way of practices at a firm.
214	Saying this over and over again will not make it true. Delete this sentence.
215	Launching an investigation as a result of a single organism is unlikely to do anything other than expend resources on a anomaly that could just as easily have been caused by the environmental sampler. Delete the sentence.
219	Relocate the material starting at the middle of line 227 to the end of the paragraph after the first sentence of this paragraph.
237	Change "substantial" to "measurable". Provided a firm can manage the differential pressures between its environments little more is needed. "Substantial" implies a higher level of pressurization than is really necessary.
238-239	Delete the sentence for the reason noted above. Firms need to be able to measure the differential and nothing more. The more numbers placed in the document the more you are stifling innovation and increasing costs for the firm and ultimately the consumer.
242	Change "strictly controlled" to "minimized" which should be the true intent.
243	Delete "continuously", it is not a universal practice especially in older and smaller facilities.
244	Delete "frequently recorded", provided it is alarmed as noted elsewhere recording adds costs for no benefit.
263	Revise to read "… particle quality after filtration should" to avoid the implication that it is intended otherwise
269	Change "sterile" to "filtered" gas, otherwise firms would be obligated to

	perform sterility testing on samples of gas taken from their critical area. Such a practice is neither practical nor meaningful. The efficacy of these filters is established via integrity testing, and use of the term "sterile" in this sentence implies more than is readily demonstrable.
271	The use of a membrane filter on autoclave air lines is of little value if the items are wrapped properly to protect their integrity.
272	Liquids that have been terminally sterilized in sealed containers are better left undisturbed until use as opposed to opened and forcing an aseptic intervention to add a filtered gas supply. Delete "and any contained liquids" or reword to specifically exclude terminally sterilized containers.
273	Change ".., continuous overpressure…" to "… positive pressure …" Provided pressure is maintained over the liquid, it need not be continuously supplied or vented as the original wording implies.
277	Change "condensate" to "condensation". The only source of this water would be condensation of water from the solution in the vessel, and not condensate from the sterilization of the system. If properly done, condensate would be removed from the filter as part of the sterilization process.
283	Change "upon" to "prior to" to allow greater flexibility of operation. Eliminate "… periodically thereafter …" Pre- and post- testing is sufficient. Firms accept the risk associated with not testing while installed, because it forces the filter to be wetted, dried and re-sterilized, in which case it would be preferable to use a new filter anyway.
292-294	Delete this sentence, testing of HEPA's in dry heat tunnels and ovens introduces a risk of fire, increases particle counts in the equipment, and introduces potential carcinogens where they will be readily volatilized.
296-335	Delete or heavily revise this entire section. The use of DOP has been eliminated in the electronics industry with no loss (actually substantial improvements) in performance. The introduction of personnel introduces orders of magnitude more microorganisms into the cleanroom environment than any slightly porous HEPA might. The use of particle counters is sufficient to characterize the performance of the filters, after all the periodic use of DOP only serves to support performance over a minimal period of time. It's actual value in maintaining cleanroom particle and microbial quality has not been adequately demonstrated. A downstream particle test without challenge is sufficient given the substantial limitations of personnel gowning to contain microorganism in aseptic environments. The only utility of DOP might be in an isolator, where human borne contamination is reduced to such an extent that the HEPA might become a meaningful source due to the absence of personnel induced contamination.
306	Delete "… performing regularly scheduled…" DOP testing shouldn't be done more than twice a year if ever.
311	DOP testing of ULPA's makes even less sense than testing HEPA's and therefore this footnote should be deleted.

330	Delete “unidirectional”, it is not needed in this context.
331	Delete “… and at a defined distance proximal to the work surface…”. This type of test while simplistic to describe is virtually impossible to reproduce. Its’ introduction would result in any number of problems for firms trying to define a new requirement for their operations, when there were criteria at the time of design, classification and initial operation. The performance of the facility as acceptable is defined better by less subjective measurements of particle, and microorganisms in the environment and on the surfaces.
332-333	Similarly this is an entirely new requirement without precedent in cleanroom operation texts. To require every initial test to be performed in a “regular” manner is excessive. This type of test should be restricted only after facility modification or filter replacement. Variability in the results of this test may have no bearing whatsoever on the acceptability of the filters for use in aseptic processing.
359	At the end of the sentence add “… to necessary activities only.”
372-373	This sentence is redundant with the one that follows it and should be deleted.
384	Change “direct” to “appropriate” which is the more correct word to use.
394	Add the following sentence at the end of the paragraph. “Whenever possible a sterilization process should be used in lieu of a disinfection / sanitization process.” Believe it or not, that perspective is overlooked by many firms.
403	At the end of the sentence add “… provided their use does not adversely impact equipment functionality.” Believe it or not firms have built lyophilizers using sanitary valves only to find they were useless as a lyophilizer.
404	Change “classified” to “Class 100 (ISO 5)”. The elimination of drains from cleanrooms is an impossibility. Properly managed they pose no significant risk to asepsis. Any firm that installs a drain certainly understands how to manage their use without compromising microbial control. Mandating their absence serves no purpose.
415	Add the following sentence. “The firm should have defined procedures for returning the facility to operating condition after shutdown periods.”
447	At the end of the sentence add “… with any part of their gown or gloves.”
452	Change to read “… movements may disrupt…” Changes to airflow cannot be readily assessed, and this is overstated as a result.
467	Change “refrain from” to “limit their”. There are times when this is necessary in the course of activities and “limit” is a better word to connote that. At the end of the sentence, change “an aseptic processing line” to “a Class 100 (ISO 5) environment”. To embrace critical environments that are not associated with a filling line.
475	Change “qualified and appropriately gowned” to “passed gowning certification”. Certification is the term more commonly used in industry.
483	Obviously the operator should change their gown in the gown room and not in the aseptic environment. However that isn’t stated, but you might

	want to explicitly state it.
486	Other than through supervisory observation, there is no ready means to "regularly assess or audit conformance of personnel". The requirement for supervision was stated earlier, but the wording here speaks to some more extensive, but undefined requirements. Either suggest some activities or leave it to firms to decide by removing this more restrictive expectation.
493	End the sentence after "… is sufficient". There is no need to make this more frequent than it already is. Personnel are monitored on each exit and that is sufficient to identify those individuals that have difficulty maintaining asepsis of their gown surfaces.
497	Change "method" to "technique"
499	This section should be expanded to include recommendations for personnel who enter the APA but do not perform aseptic processing activities.
513-514	The benefits of this testing is by no means clear, as there already is a general restriction on allowing the any gown surfaces to contact sterile surfaces. That this reference was prepared by 2 (at least at the time) FDA individuals suggests that it is more of a new regulatory requirement than a common, and most importantly useful, practice,
548	Delete "and" and replace with "/". Crystallization and precipitation are different methods for bring something out of solution. Crystallization is usually the result of physical changes to the material while it is in solution, while precipitation is the result of a chemical reaction that renders it insoluble in the liquid. They are not sequential steps of the same process.
552	End the sentence after "… steam sterilization." The remainder of the sentence is unnecessary detail.
556-557	This section relates to components and is not the appropriate location to provide guidance on sterilization in the same form as that which appeared earlier in the document. Delete this sentence.
564-567	This section is improperly located within this section and should be moved Section VII of the document. It is largely redundant with the information provided in the section.
582-583	The suggestion that the rinse water be of high purity is useless unless a specific quality of water is required to be used. In the absence of a defined requirement this sentence should be deleted.
592	At the conclusion of this paragraph add the following sentence. "Where depyrogenation by heat has been demonstrated, sterilization confirmation is not required."
594-598	Delete this material, as it is placed in the wrong section of the document. It should be relocated to section IXc.
601-605	Delete this material, as it is placed in the wrong section of the document. It should be relocated to section IXc.
613-615	Delete this material, as it is placed in the wrong section of the document. It should be relocated to section IXc. Reference to XIc as provided at

	the end of the sentence is in error.
618-620	Why is special attention drawn to silicone in this sentence. All materials used in conjunction with pharmaceutical manufacturing should be subject to the quality control program.
622-625	Relocate this to section IXc.
635	Delete the portion of the sentence after "… machinery." Once the materials leave the control of the manufacturer, mishandling by others is not an indication of an aseptic processing problem at the firm.
639-640	The appropriateness of the firms AQL's for container system components is only remotely connected to the ability of the firm to aseptically process the product. Component selection, quality assurance and its impact on container-closure integrity are separate subjects and should not be confused with the aseptic processing. While this may be acceptable guidance it applies to all types of sterile products, as well as a number of non-sterile ones as well, and should not be included in a technology specific guidance such as this one.
708	Change "processing" to "filling / sealing" as the guidance in this section is only relevant to final product containers. The broader term of aseptic processing addresses the subject in the full context including manufacturing, and is not covered in this section of the document.
724	Change "issues"" to "worst case conditions". The application of 'worst cases' in the validation of aseptic processing is commonplace, and its use in this section makes the intent clearer.
727-728	Delete the portion of the sentence after "… atypical interventions". Each of the items listed is a particular type of atypical intervention and providing a list is unnecessary.
741-742	The intent of this sentence is unclear, what are you expecting the firm to define in its' procedures?
746	The sentence at the end of this paragraph presents an extremely biased perspective on aseptic activities. On what basis is a practice to be considered acceptable if not via a media fill? As written, it allows for a subjective decision to deem a process unacceptable when the evidence directly supports its acceptability. A 'good practice' cannot be considered acceptable when it cannot be supported by a process simulation, thus there is no reason to invalidate a so-called 'bad practice' that is defendable by successful simulation. If a bad result damns a practice, a good one must result in the opposite conclusion.
746	A requirement should be included for firms to provide a written rationale for their selections throughout the design of the media fill program. The rationale serves to document the decisions made by the firm in its media fill program.
775	The imposition of additional monitoring as required in this sentence introduces additional interventions to the process that may result in an increased potential for contamination. Adding new environmental testing because of an inconclusive investigation could thus result in increased

	risk to the patient. The sampling of an environment must be recognized as an aseptic intervention that has the potential for the introduction of microbial contamination.
792	Change the sentence to read "… actual manufacturing process *performed by each individual* to best simulate …". If the same process is carried out sequentially by a number of operators who each perform the same task, then the duration of concern should be that associated with the duration of a single operators work interval.
806	Change to read "… should *exceed* the maximum…" Media fills larger than the batch size establish the acceptability of smaller size batches. Making a requirement for an 'equal' size simulation is of no value and presents operation difficulties should a vial break during the simulation. PDA TR#22 provides a substantially better presentation of this subject than is provided here.
825-829	While the intent is to clarify what line speed to run for which reason, there is no clear indication what the firm is expected to do, especially in the initial media fills for a line. Clarify your initial and on-going requirements
880	Delete "amber or other opaque" from the sentence. Amber glass has been successfully utilized in a number of media fill programs. Provided the firm can demonstrate that it can detect microbial contamination there should be no requirement to purchase clear glass solely for the purpose of conducting the media fill.
883	Firms should always conduct a thorough inspection of the filled units immediately after completion of filling / sealing. Non-integral units culled at this point do not count as part of the media fill, but an identical unit discovered incubation would. All units should be inverted briefly prior to incubation to ensure contact between the media and the container-closure surfaces.
896	Firms should be allowed to clear units between easily identified locations on the filling line. In some cases the number of vials between these points may vary, as the line may not be completely filled with vials. Thus the same intervention may not result in exactly the same number of vials being removed each time. Minor differences such as these should be accepted as something that cannot always be performed in an identical manner each time. Revise the sentence to read "… quantity of units removed, *location of removed units*), provided …"
904-907	The intent of these sentences is not sufficiently clear. Revise to clarify the concern, and the expected practice.
922	Delete "all" as it implies exhaustive evaluation beyond any reasonable effort.
923	Change "effects" to "potential implications" to clarify the expected intent.
928	Provided that the percentage of contaminated units is low enough there is no reason not to accept a "directly proportional" relationship between the numbers filled and the number of positives detected. This practice by itself is not objectionable. Moreover in light of the acceptance criteria

	provided in this document it reflects a more realistic perspective of what might occur. While the goal is always zero for a media fill, some allowance must be allowed for an occasional positive in larger media fills. Anything else would likely result in firms doing smaller media fills as the allowed contamination is a higher percentage of the total number filled. This is a likely unexpected consequence of the statement and represents a step backward. Larger media fills reflect a better simulation of the production process and firms should not be penalized for performing them as the document states.
935-944	The acceptance criteria penalize firms that produce media fills larger than 10,000 units and needs to be revised. Recognize also that firms are unlikely to produce a media fill of less than 10,000 vials unless that number represents an unusual burden. In addition, the acceptance limits for media fills should not be different for different size lots. The presence of a single positive vial in a media fill of either 5,000 or 10,000 units should not result in an investigation. Finding an assignable cause for such a low incidence of contamination is a virtual impossibility, and would serve no purpose. As defined in the guidance, it appears that only media fills without any observable contamination are acceptable. The PQRI survey in a very small sample size indicated that 9% of all media fills had at least one contaminated vial. To require investigations for nearly 10% of all media fills is excessive.
956-958	Media fills are not a direct measure of the sterility assurance afforded to any batch. Their success or failure may be wholly unrelated to batches produced immediately before or immediately after a failed media fill. As the majority of contamination in an aseptic processing environment is personnel related, intimations of linkage between the media fill and production lots may be spurious. Each intervention, each filling day, each set-up has to be considered as individual isolated activity that may have no connection to other events. Were media fills to be contaminated via non-human sources (something which is decidedly not the case) linkage might be possible. Media fills demonstrate a capability, and are not definitive evidence of anything more. Their success while suggestive is not definitive, therefore their failure should also not be considered as conclusive evidence of a widespread contamination problem.
969	Delete the sentence beginning on this line. The pore size is only one aspect of filtration effectiveness, and filters of pore sizes larger than 0.2 um can reproducibly provide a sterile effluent.
970-972	The determination of exact microorganism size in the product fluid is a virtually impossible task. There are no methods that can be used to this determination and thus the recommendation is worthless. Moreover filters retain organisms by mechanisms other than size elimination as suggested by this sentence. Delete it as misleading, erroneous and technically unattainable.
975	Fixation on a single microorganism and a single pore size represents an

	overly simplistic view of membrane filtration. The document should support greater flexibility of practice and a better understanding of the realities of membrane filters.
978-980	While use of a bioburden isolate sounds appealing as directly supportive of the filter / fluid relationship it is an extremely arduous task well beyond the capabilities of most firms. The microbial challenge of filter using introduces often introduces such substantial compromises to the filtration process that any connection to the process situation is limited.
985-987	Pre-filtration bioburden information, especially as it results to the size of microorganisms, is by no means a universal practice. This represents a new requirement for many filtrations whose overall benefit to the consumer is unknown.
989-990	Direct inoculation of *B. diminuta* into process fluids without change to the organism's size is almost impossible. The microbial challenge studies included as a part of submissions often alter the conditions of the filtration / fluid so greatly as to make any meaningful conclusion as to validity of the result largely speculative.
1001	This entire discussion of filtration validation must indicate that the filters being evaluated must be sterilized in the same manner as will be used in routine operation when evaluated in any of these studies whether for compatibility or microbial retention.
1018	Delete "… (membrane or cartridge)…" While the intent of this is laudable there are instances where this cannot be carried out to the fullest extent. For example, where only a limited amount of solution is available, the use of a cartridge is impossible. Scale down / scale-up will introduce differences in materials of construction for cartridges that are unavoidable. Perhaps a modifier such as "… whenever possible." Should be added at the end of this sentence.
1038	Delete "heat" as the concepts are broadly applicable to all forms of sterilization.
1045	Change "product's" to "equipment's" to more accurately reflect what is being protected.
1050-1052	Delete the last sentence in this paragraph. It has been demonstrated by many different firms that position in the load for parts sterilization is irrelevant. This is an inappropriate carryover from terminal sterilization and should be deleted.
1060-1101	Delete these paragraphs in their entirety as they attempt to cover the entire subject of steam sterilization in a single short section. The subject is far too complex for that brief a section. Eliminate this detail and direct the reader to appropriate and detailed references where substantially more information is available. Inserts like these in the body of the document serve no real purpose. Resume with the reference to the submission guidance, near the bottom of the page.
1117-1118	Delete this unnecessary requirement. The in-house determination of D-values is by no means a trivial task. Where a firm purchases an indicator and uses it as described by the supplier it should not be

	required to perform a D-value measurement. D-value measurements at outside laboratories are of no significant value if the biological indicator is tested in-house, the vendor's data is just as acceptable. A meaningful requirement would be the following: Determination of microbial resistance and population should be performed for any biological indicator inoculated onto a substrate or used as other than described by the vendor. D-value determinations can be conducted by an independent laboratory.
1125-1133	Delete this paragraph for the same reasons described above for lines 1060-1101
1145	Delete "meaningful" from the sentence. The absence of recoverable microorganisms from the aseptic environment in the vast majority of samples means that in the context of this document the only 'meaningful' results are those employed to cast suspicion on the process. The recovery of an occasional organism from the aseptic environment is not a 'cause celebre' that will result in rejection of the materials being processed.
1147	Change to read "… well as *possible* environmental trends …" Expectations of trends where there are rarely recoverable organisms is a carryover from prior years when microbial levels in the aseptic environment were substantially higher. In recent years trends are essentially non-existent in Class 100 environments, they may be detectable in non-aseptic environments outside the aseptic suite.
1147-1149	Delete this sentence, as there are few indications of the route of contamination introduction, especially when the counts in the critical zone are already so low. Moreover since the majority of counts are personnel related, there is very little to be gained in pursuing exhaustive investigations in pursuit of sources when the major source of contamination in the aseptic area are the personnel who must be present.
1152 & 1158	Delete "and scientifically sound methods", it implies a precision to the measurements that is simply unattainable in microbial monitoring. There are few published papers addressing the 'scientific nature' of these monitoring systems let alone anything that supports their utility in monitoring aseptic environments.
1178-1180	Curious that the document makes a point of mentioning "false negatives" when the perhaps more likely circumstance of 'false positives' derived from the person sampling the environment is not mentioned at all. This paragraph should offer a balanced perspective considering that both situations are perhaps equally likely especially when very low levels of contamination are prevalent.
1182-1184	The phrase "In the absence of any adverse trend …" represents the routine situation as opposed to a unique circumstance. As such this paragraph represents a slanted perspective on environmental monitoring. To suggest as this paragraph does that a single result above an action level (usually NMT 1 in the critical zone) forcing an in-

	depth investigation, and remedial measures. The approach is inconsistent with current performance of aseptic processing facilities. This guidance will result in a substantial number of 'witch hunts' as firms are forced to find conclusive evidence to support continued operation. It must also be recognized that the action levels in these areas are largely developed by regulators and do not reflect the actual results of any individual firm or operation. Expectations of zero counts in the critical zone are nice, but when an occasional organism is detected (as it must be) it should not be considered a surprise, nor worse yet a reason for rejection. Aseptic environments strive for the attainment of sterility, yet cannot attain that state regardless of how many guidelines and 483 observations suggest that it might.
1199	Delete "published" as the only data a firm might have would be its' own that is unlikely to be published. Any published data it might find is also likely to be inappropriate for another firm with different facilities, processes, disinfection regimens, monitoring methods, etc.
1203-1204	Modify the sentence as the adoption of 'alert' levels is not possible within Class 100 aseptic environments where the 'action level' is typically NMT 1 CFU per sample.
1205	The averaging of results from environments is an expectation of EU Annex 1 (section 5 explicitly states 'These are average values'). For the major regulatory bodies in the world to have such diametrically opposed views is unacceptable. Given the expectations of 'sterile conditions' so frequently stated in this guidance it is evident that FDA's views with regard to microbial monitoring practice is at odds not only with industry but also with EU requirements.
1212-1213	Change "Trend" to "Periodic" at the start of the sentence as 'trends' are a rare occurrence and the expectation should be for periodic reporting which a 'trend' report would not provide.
1220	Change "trends" to "results" as 'trends' are not common enough.
1229	Change "limited" to "defined" which meets the same intent but allows firms flexibility to support longer expiration dating. Firms should be allowed to establish the dating period and provided it is adequately supported, there is no reason to imply that the period is 'limited'.
1248	The inclusion of "floors" as the second item on this list is unfortunate. Counts on floors are undoubtedly going to be the highest in an environment, however their importance as a source or harbor of contamination in an aseptic processing suite is overrated. Microorganisms are barely motile and even those that are would be hard pressed to move 5 times their length. Note also that this guidance makes no distinction between any surfaces in the aseptic core as being any more or less significant than any other clearly implying that the alert (if present) and action levels should be the same. Monitoring of ceiling surfaces is rare and while it could possibly be important, it is unclear how any microorganism could possibly proliferate on the ceiling. The monitoring of ceilings is problematic in that it may require operators to

	bring their feet to a level above the floor a potentially risky process.
1257	Revise the text to read "… all allow *semi*-quantitative testing …" The variation in sampling methods, and measurement duration, among the various devices makes any claim of 'quantitative' measurement of the microbial levels in very clean environments such as found in a Class 100 aseptic environment unrealistic in the extreme.
1264-1265	Delete the last sentence as it suggests that these samplers can be evaluated quantitatively and that this is a requirement for their selection. Given the inability of these units to be 'calibrated' or 'standardized' in the sense that non-microbial sampling systems can be, this sentence asks for the impossible.
1269-1279	Despite the biased perspective given in this guidance settling plates are widely used in the industry and required in EU Annex 1. Their inability to 'quantify' microorganisms in Class 100 environments is not a real disadvantage as any count in these environments is a decidedly rare occurrence. Their placement in proximity to aseptic operations without interference to the airflow is a decided advantage, and allows for essentially continuous sampling without adverse impact. Settling bottles are widely used in isolators and offer similar advantages. Revise the entire paragraph to provide balanced treatment of the subject. Add the following sentence at the end of a revised paragraph – "Settling bottles have proven highly effective in isolators are do not desiccate appreciably over even extended exposure periods.
1284	Change "often" to "may". Incidences of microbial contamination in aseptic processing environments, media fills and even sterility testing are becoming some unusual that correlation is unlikely. Perhaps the only coincidence in all of these is that the isolates are predominantly of human origin.
1310	Change to read "… on all lots of *in-house* prepared media." Testing commercially prepared media is of little value as the suppliers have already evaluated the media against both EP & USP organisms. Testing in-house isolates is similarly not necessary as these were originally detected on the same media.
1316-1320	Adding a requirement for pre-filtration bioburden sampling including in-process limits increases the cost of medication without enhancing patient safety. There are no incidents of sterility failures associated with penetration of filters by bioburden organisms.
1330-1334	Relocate this section to IVA, or eliminate if it is redundant with existing guidance in that section.
1339-1498	Delete this section in its entirety, as the subject has been more completely addressed in other documents. This treatment serves no useful purpose except to perhaps confuse the reader as to which of the many possible positions on this are to be followed. If FDA wants to issue new guidance on this subject it should issue separate guidance on this subject alone as it would be relevant to terminally sterilized pharmaceuticals, biologics and medical devices.

1395-1396	Requiring that sterility test samples be taken in conjunction with interventions is an impossible requirement. Given that firms are required to remove potentially contaminated units reproducibly during media fills and production batches, there really are no units that could be sampled to satisfy the requirements of this testing anyway,
1430-1431	This sentence introduces the subject of trends as being relevant to sterility testing. There is little evidence to support this position. Trends are nowhere as predominant as the authors of this guidance apparently believe.
1442	Clarify the phrase "investigate globally". The intent of such an investigation is unclear, how could one ever stop?
1461	Add the following statement – "Aseptically produced items prepared in an isolator should be tested in an isolator."
1476	Change "strongly indicate" to "suggest". Personnel borne contamination is certainly a major factor in environmental monitoring but beyond that there is little that can be directly inferred from microbial recovery from personnel. That they will occasionally be found to have microorganism on them should be expected, and by itself doesn't help resolve contamination problems.
1490	Data from HVAC (other than EM results) and WFI systems are unlikely to be useful in the investigation of sterility test failures. Adding unusual items such as these allows investigators to cite firms for inadequate investigations despite their having looked at all relevant information.
1512	The scope of this review is excessive as noted above. All of the systems within a facility are subject to various monitoring and control mechanisms. In consideration of release decisions report by exemption is a more approach. That's not to say that the less directly impacting systems are ignored, its just they play a secondary role in that decision. For instance difficulties with the water system would be known to the facility management and unless there is an issue with the lots produced individual review of water data would not normally take place.
1520-1522	This sentence is stated as if were established fact, rather than an opinion of the author. There is no available data to support this contention. Delete the sentence.
1522-1527	This information is not directly relevant to batch record review. It is also redundant with information provided in section IXA. Delete this material.
1535	Change "line" to "environment" to more accurately reflect isolation technology in a broader context.
1546-1552	The concern with regard to leaks in isolators is overstated. Cleanrooms operate on the principle of leakage from the clean to the less clean environment. The situation with isolators is identical to this and does not present an extraordinary concern with regard to contamination.
1549	Delete "gloves" and change "daily" to "periodic" to reflect more accurately the degree of concern that is associated with leaks in isolators. There is no comparable requirement in cleanrooms and thus there should be no special requirement for leak testing in isolators. Glove integrity is the

	subject of the next paragraph.
1551-1552	Change "… before they fail or degrade." to "… as necessary." The negative tone of the original wording is inappropriate.
1556-1566	This section presents a biased perspective relative to gloves used in isolators. Failure of gloves on gowned personnel certainly occurs with perhaps greater frequency and given the more fragile construction should receive comparable attention. Raising this as a concern with isolators without a comparable concern for gloves on aseptic gowned personnel suggests that isolators are less capable than manned cleanrooms. If FDA is to avoid being an obstacle to the implementation of what is most certainly a more reliable and safer means of aseptic processing using isolators, then this guidance has to acknowledge that isolators are less risky than manned cleanrooms. There is no comparable text on either gown or glove integrity for manned cleanrooms and thus this section sends the wrong message. This document should favor isolators and the continued inferences that isolators have "special" problems that make them less capable is a major flaw in this document.
1560	Change "Mechanical" to "Physical". The tests that are used are physical tests of integrity not strength of the materials. Note that nothing is stated in the document regarding leak testing of cleanroom gloves where a similar concern must exist but is ignored in this guidance.
1564-1566	Delete this sentence. Here again, the guidance goes to extraordinary lengths to make it appear that isolators are less capable than manned cleanrooms. This is clearly a wrong perspective for the FDA and industry to have to deal with.
1577-1582	Delete the first 3 sentences in this paragraph. There is no evidence to support that unidirectional flow is of any benefit in isolators, whether open or closed. The application of unidirectional air is derived from experience with manned cleanrooms, and there is no reason to believe that it has any value at all within isolators. To avoid inhibiting the further development of this technology this guidance should not provide engineering guidance where there is no clear rationale for it to do so. The less speculative guidance this document provides on a technology that has demonstrated superior performance to manned cleanrooms the better the document will be.
1593	Change "an open exit portal" to "openings". Open isolators have openings used for the in-feed of materials as well.
1598-1599	End the sentence after "… on the system's design." The additional clause is not necessary as the design includes all elements of the system.
1604-1605	Delete this sentence that offers nothing in the way of constructive information in the paragraph. The stated premise is one offered by MCA several years ago and was speculative then, and is speculative now. Most firms using open isolators are fully cognizant of the importance of protecting the internal environment from the ingress of contamination

	from the surrounding area. Recognize again that this situation exists with ordinary cleanrooms, but the concern is only voiced for isolators.
1611	Note that ISO 5 does not include velocity or unidirectional requirements. Rigid specifications for velocity or mandates for unidirectional flow are not a part of ISO cleanroom standards. I doubt this is the view of FDA especially as stated in this document but it is accurate.
1615-1616	Delete this sentence. There are a number of FDA approved installations where there is no classification of the surrounding environment. Properly managed there is no reason for this 'requirement' in this document. Instances where FDA inspectors observed deficient procedures at one or more firms and want to mandate a blanket solution that penalizes all installations. Properly operated an unclassified surrounding to the isolator is not a risk whether the isolator is open or closed.
1637-1640	Delete this entire section. It is redundant with earlier guidance on lines 1602-1607.
1655	Delete "vaporized" to accommodate agents such as chlorine dioxide and ozone that are gases.
1656	Delete "although these agents have limited capability to penetrate obstructed or covered surfaces." No agent has the ability to penetrate these types of situations and inclusion of such a statement is another attack on isolators. The treatments afforded in manned cleanrooms are certainly less effective, and yet there is no comparable concern raised in the body of the document. The entire subject of facility disinfection for manned cleanrooms is not mentioned in this document, and there can be no question that those practices are less reliable than the decontamination treatment of isolators.
1657-1659	Delete this sentence. Fraction negative studies are the only way to establish the lethality delivered by the agent. The referenced paper does not support the position taken in this guidance document.
1660	Delete "… on various materials and …" The objective of the decontamination is exactly that and should not be made more restrictive than a sterilization process. The validation of sterilization processes does not require inoculation on multiple substrates, and given the lesser objective of the decontamination processes applied to isolators should not be considered a requirement.
1664	Delete the footnote it supports an unrealistic expectation as noted above regarding decontamination procedures.
1668-1669	Delete this sentence. Multipoint determination of decontaminating agent concentration is prohibitively expensive. In addition, given that the dominant agent vaporized Hydrogen Peroxide must condense when it encounters a cold surface internal to the isolator, the measurement of concentration in the gas phase may be of little relevance. In many instances, the proper conditions for decontamination will result in concentrations that 'blind' these sensors due to condensation on their lenses. PIC/S added this 'requirement' without consideration of the real science behind vaporized Hydrogen Peroxide so citing PIC/S as a

	source is irrelevant.
1676	Delete "… include a built-in safety margin and …" Were this process to be considered a sterilization this might be a reasonable expectation. Forcing in on a decontamination procedure is not necessary. All of the commentary in this section has the effect of making isolator technology harder and more restrictive to use than a conventional manned cleanroom. The wrong message is being sent by FDA in this guidance.
1686	Change to read "Product Contact Part Sterilization". That more accurately reflects the true subject of this paragraph. The original title can be construed to require sterilization of the isolator internals.
1689	Clarify the term "loose materials" in this sentence. There are no "loose materials" in most aseptic filling operations.
1698-1700	Add a cautionary statement regarding avoiding leaving media residues inside the isolator as a result of the environmental monitoring. Isolators are generally hostile environments for microorganisms, and if in the monitoring nutrient media residuals are left behind it can adversely impact the performance of the isolator.
1700	Delete "Air quality should be monitored periodically during each shift." There should be no differences in environmental monitoring frequency in an isolator relative to a manned cleanroom, thus the general EM guidance provided else should prevail.
1708-1710	Delete this sentence. Certainly the same situation prevails in a manned cleanroom where gowned person (who are most definitely not sterile and whose gowns are not hermetically sealed) must perform aseptic interventions, yet there is no mention of this as a concern in that section of the guidance. The guidance should not discourage the use of isolation technology yet it consistently does so throughout this entire appendix.
1715	Add "Form-Fill-Seal" to the scope of this appendix. It's a closely related process and could be treated with minimal revisions.
1738	Change "sterile" to filtered". Demonstration of sterility for any item is difficult to prove. Changing to "filtered" makes a more appropriate statement.
1779-1781	Delete "product-plastic compatibility" and "unit weight variation" as these are not directly related to maintenance of sterility.
1795-1796	Delete "… container weight variation, fill weight, …" as these have no relevance for aseptic processing.
1798	Correct word error "filing" to "filling".
1798	The use of the term "continuous monitoring" has been raised as a concern in the recently modified EU Annex 1. Clarify the intention with regard to 'continuous' in this guidance.
1815	Correct spelling error "sterlyze" to "sterilize".
1821	Delete "should" at the start of this paragraph as there are no requirements in this opening sentence.
1832	Add the following sentences, "Proper process design can substantially reduce the potential for ingress of microbial contamination. The process

	should be designed to minimize interventions of all types that could adversely impact the sterility of the equipment / materials being processed."
1838-1839	Change to read "Microbial surface *and personnel monitoring* should be performed at the end of operations … " Delete the last sentence in the paragraph which could be interpreted as requiring personnel monitoring during the process.
1854-1855	PDA TR #28 has some relevant guidance to assist in the design of the simulation studies.
1858-1870	This section presumably says something different in relation to these products, however the operating principles, design objectives and other elements are the same as those noted in the earlier portion of this appendix. Attempting to distinguish between them and make unique requirements for these products is inappropriate. Moreover the suggestion that some specialized tests indicated in lines 1869-1870 could somehow have relevance to aseptic processing is highly speculative.
1874-1875	If ISO is to be cited, then that guidance document should adhere it completely. There are many instances in this guidance where it differs from the ISO standard. As ISO 14644 is a US requirement no deviations should be present in this guidance.
1876-1877	That this document had to reference a 26 year old document says a lot about the perspectives of the authors of this document. Current thinking with regard to aseptic processing is decidedly different today than it was in 1967. The stated belief may be true for large particles that might have been found in large numbers in the cleanrooms of that era. Today's cleanrooms and isolators are largely devoid of large particles and thus the inference from so many years ago is hardly relevant any longer in Class 100 environments.
1878-1879	Curious that the reference chosen to support the need for unidirectional air predates FS209C that abolished it in 1987. That no non-healthcare cleanroom standard since that time has included a unidirectional flow requirement speaks volumes. Current practices for cleanrooms in all other industries are substantially different from those of 1972, and yet unidirectional airflow persists as a Class 100 only within the pharmaceutical industry perhaps largely because of FDA's denial of the realities learned elsewhere.
1910	The reference list is deficient in that many excellent references are not cited. These references provide substantial more complete information on many of the subject addressed in this document. The PDA alone has published several excellent guidance documents on relevant subjects. PDA's Technical Reports #'s 1, 2, 13, 22, 26, 28 and 36 all provide useful information on the subjects of this guidance.
1931-2059	The glossary provided with this document provides a number of definitions that are inconsistent with more prevalent and long standing definitions used elsewhere. Wherever possible, the guidance should

	utilize pre-existing definitions in common usage. Examples include: asepsis; biological indicator; critical surfaces; decontamination; dynamic; d-value; endotoxin; isolator; closed isolator; open isolator.
1931-2059	The glossary fails to define some essential terms associated with aseptic processing. Missing definitions include: sterile; SAL; PNSU; sterilization; pyrogen; static; routine intervention; non-routine intervention.
1931-2059	The glossary defines terms in a manner that is inconsistent with statements made in the body of the document. Examples include: sterilizing grade filter;
1931-2059	There are definitions in the glossary that should be deleted as not required in this guidance. Examples include: laminar flow (out dated concept replaced by unidirectional airflow); HVAC (common use); HEPA (common use)