Comments on: "Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice, Draft Guidance"
Docket No. 2003D–0382

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Line Number	Suggested Change	Rationale
81	Because there is no process to sterilize the product in its final container, it is critical that containers be filled and sealed in an aseptic environment.	The term "extremely high-quality" is unclear and undefined.
87	Each of these processes requires thorough validation and control. Delete "aseptic manufacturing."	These are sterilization, not aseptic manufacturing, processes.
91	A terminally sterilized drug product, on the other hand, usually undergoes a single sterilization process in a sealed container, thus limiting the possibilities for error.	There may be more than one sterilization process.
95	Delete "Manufacturers should have a keen awareness of the public health implications of distributing a nonsterile product. Poor CGMP conditions at a manufacturing facility can ultimately pose a life threatening health risk to a patient."	Manufacturers are well aware of this fact, and it is unnecessary to include it in the guidance.
114	In such cases, a manufacturer can explore the option of adding adjunct processing steps to increase the level of sterility assurance.	"Sterility assurance" is an accepted and understood term.
164	This area is critical because the product is not sterilized in its immediate container and is vulnerable to contamination during processing. Delete "processed further."	Clarification.
167	Particles are significant because they can act as a vehicle for microorganisms. Delete "enter a product and contaminate it physically or, by acting" and "biologically."	Environmental particles are too small to "contaminate" a product physically. Visual and machine inspection would not detect the presence of these particles in the unlikely event they

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		were to find their way into the finished product.
177	Delete "Deviations from this critical area monitoring parameter should be documented as to cause and significance."	This is covered in other sections of the document and is inappropriate in a "definition."
180	Measurements to confirm air cleanliness in aseptic processing zones should be taken at the sites where there is most potential risk to the exposed sterilized product and container-closures. Delete "with the particle counting probe oriented in the direction of oncoming airflow and."	It may be inappropriate, in some cases, to orient the probe in the direction of the airflow.
196	Air in critical areas should be HEPA-filtered unidirectional flow air at a velocity sufficient to sweep particles away from the filling/closing area and maintain unidirectional airflow during operations. Delete "supplied at the point of use as" and "laminar." Delete footnote 4.	"Supplied at the point of use" is overly restrictive and the term "laminar" is incorrect. Unidirectional airflow in isolators may not be necessary or desirable; likewise the requirement to maintain 0.45 to 0.51 m/s velocity.
234	Adequately separating areas of operation is an important part of contamination <u>control</u>. Delete "prevention."	Clarification.
236	Rooms of higher air cleanliness <u>generally</u> should have a positive pressure differential relative to adjacent rooms of lower air cleanliness. Delete "substantial."	"Substantial" is undefined and unnecessary in this context.
238	Delete "For example, a positive pressure differential of at least 12.5 Pascals (Pa)[5] should be maintained at the interface between classified and unclassified areas. This same overpressure should be maintained between the aseptic processing room and adjacent	Overly specific.

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	rooms (with doors closed). 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 (Ref. 4)."	
249	For areas of higher air cleanliness, higher air change rates will provide an increased level of air purification. Delete "significantly."	"Significantly" is undefined and unnecessary on this context.
268	Delete "Membrane filters allow the filtering of compressed gases to meet an appropriate high-quality standard."	Redundant.
272	Sterilized holding tanks and any contained liquids <u>may</u> be held under continuous overpressure to prevent microbial contamination. <u>In that event,</u> safeguards should be in place to prevent a pressure change that can result in contamination due to back flow of nonsterile air or liquid. Delete "should."	Clarification.
292	Among the filters that should be leak tested are those installed <u>in the cooling zone(s)</u> in dry heat depyrogenation tunnels commonly used to depyrogenate glass vials.	Due to the flammability of DOP and other materials commonly used to generate an upstream challenge, these materials should not be used for filters in the hot section of the tunnel or oven.
296	Dioctylphthalate (DOP) and Poly-alpha-olefin (PAO) are examples of appropriate leak testing aerosols. <u>Other, equivalent materials may be used. Leak testing aerosols should not promote microbial growth.</u> Deleted "Any aerosol used for challenging a HEPA filter should meet specifications for critical physicochemical attributes such as viscosity." Deleted "Some alternative aerosols are problematic because they pose the risk of	Clarification.

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	microbial contamination of the environment being tested. Firms should ensure that any alternative used does not promote microbial growth."	
302	An efficiency test is a general test used to determine the rating of the filter. Delete "only."	Clarification; the test also detects "leaks."
307	The challenge typically is conducted using a polydispersed aerosol usually composed of particles . . . approximately 0.3 microns. Delete "should be."	Changed to provide needed flexibility.
310	Performing a leak test without introducing a sufficient challenge of particles of known size upstream of the filter may be ineffective for detecting leaks. Delete "upstream" and "is."	Redundant use of the term "upstream." Changed to provide needed flexibility.
326	Delete "HEPA filter leak testing alone is not sufficient to monitor filter performance. This testing is usually done only on a semi-annual basis. It is important to conduct periodic monitoring of filter attributes such as uniformity of velocity across the filter (and relative to adjacent filters). Variations in velocity generally increase the possibility of contamination, as these changes (e.g., 329 velocity reduction) can have an effect on unidirectional airflow. Airflow velocities are measured 6 inches from the filter face and at a defined distance proximal to the work surface for HEPA filters in the critical area. Regular velocity monitoring can provide useful data on the clean area in which aseptic processing is performed. HEPA filters should be replaced when nonuniformity of air velocity across an area of the filter is detected or airflow patterns may be adversely affected."	The paragraph is misleading. There is little evidence that the velocity uniformity of a HEPA filter changes with time. The recommendation to measure the velocity uniformity 6 inches from the filter face and at a defined distance proximal to the work surface is confusing. Finally, there is no recommendation regarding how much non-uniformity is acceptable.
337	Although contractors often provide leak testing and efficiency testing services, drug manufacturers are responsible for ensuring	Clarification.

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	that these essential certification activities are conducted satisfactorily. Delete "vendors" and "these."	
348	Change "sterility" to "sterility."	Typographical error.
372	To prevent contamination, partially closed sterile product should be transferred only in critical areas unless this transfer is accomplished in closed containers designed and validated for this purpose.	Closed transfer containers can protect the product from contamination.
378	Carefully designed curtains, rigid plastic shields, or other barriers should be used in appropriate locations to achieve segregation of the aseptic processing line. Delete "significant."	The term "significant" is superfluous and undefined in this context.
385	Airlocks and interlocking doors facilitate control of air balance throughout the aseptic processing facility. Delete "better."	The term "better" is superfluous and undefined in this context.
387	Other interfaces such as gowning areas are appropriate locations for air locks. Deleted "personnel transitions or material staging."	Clarification.
396	Examples of adequate design features include seamless and rounded floor to wall junctions and corners. Delete "as well as readily accessible."	The term "readily accessible" is vague and undefined.
403	With rare exceptions, exposed drains are not considered appropriate for classified areas of the aseptic processing facility.	Drains in Class 10,000 and 100,000 areas are appropriate as long as their use is adequately controlled and the areas are protected from backflow.
408	The effect of equipment design on the cleanroom environment should be considered. Ledges should be avoided. Delete "addressed."	Clarification. Vertical flat surfaces are appropriate.

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	Delete "Flat surfaces." Delete "that accumulate particles."	
424	To ensure maintenance of product sterility, operators involved in aseptic manipulations should practice good aseptic technique at all times. Delete "adhere to the basic principles of."	Clarification.
427	Appropriate training should be conducted before an individual is permitted to enter the aseptic processing area. Delete "and perform operations."	Training is required whether or not an individual is to "perform operations."
433	Similarly, the quality control unit should provide regular oversight of adherence to established, written procedures and good aseptic technique during manufacturing operations. Delete "basic" and "techniques."	Clarification.
470	• Maintaining proper gown control Delete "Proper Gown Control"	Formatting consistency.
476	An aseptic processing area gown should provide a barrier between the body and exposed sterilized materials and minimize the release of particles generated by, and microorganisms shed from, the body. Delete "prevent contamination from."	Clarification. Conventional gowns used for aseptic processing do not prevent the release of human-borne contamination.
489	Gowning qualification should include microbiological surface sampling of several locations on a gown (e.g., glove fingers, facemask, forearm, and chest). Delete "other sites."	Clarification.
493	Delete "Semi-annual or yearly requalification is sufficient for automated operations where personnel involvement is minimized."	Specification of frequency is overly restrictive and unnecessary in light of the statement in the previous sentence, "periodic requalification should

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		monitor various gowning locations over a suitable period to ensure the consistent acceptability of aseptic gowning techniques."
496	Delete "To protect exposed sterilized product, personnel should be expected to maintain gown quality and strictly adhere to appropriate aseptic method. Written procedures should adequately address circumstances under which personnel should be retrained, requalified, or reassigned to other areas."	Redundant.
542	In aseptic processing, each component is sterilized or several components are combined, with the resulting mixture sterilized. Delete "individually."	Clarification.
551	Delete "If a component is not adversely affected by heat, and is soluble, it can be made into a solution and subjected to steam sterilization, typically in an autoclave or a fixed pressurized sterilize-in-place (SIP) vessel."	If this were possible, it would make more sense to conventionally fill the solution and terminally sterilize the filled product.
560	Such methods should be carefully controlled and validated if used for powders . . . and to minimize residual ethylene oxide and <u>sterilization</u> by-products.	Clarification.
595	Validation of dry heat sterilization and depyrogenation should include appropriate <u>temperature distribution</u> and <u>heat penetration</u> 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.	Correction.
600	Pyrogen on plastic containers can be generally removed by multiple WFI rinses. <u>Validation data from the rinsing procedure should demonstrate successful endotoxin removal from plastic materials.</u>	Inserted for consistency with the paragraph on rubber closures. In practice, plastic containers are rarely depyrogenated. Suggest

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		deletion of this recommendation.
608	At minimum, the initial rinses for the washing process should employ recycled WFI from subsequent stages of the washing process or Purified Water, USP, followed by final rinse(s) with WFI for parenteral products. Delete "of minimal endotoxin content."	Many washers use recycled WFI for initial rinses. As originally proposed, this would have required endotoxin testing of Purified Water, USP.
622	Delete "Contract facilities that perform sterilization and/or depyrogenation of containers and closures are subject to the same CGMP requirements as those established for in-house processing. The finished dosage form manufacturer is responsible for the review and approval of the contractor's validation protocol and final validation report."	This goes without saying. If necessary, it could be moved to the "Scope" section of the document.
658	Adequate cleaning, drying, and storage of equipment provide for control of bioburden and prevent contribution of endotoxin load. Delete "provides" and "prevents."	Grammar.
678	Delete "Maintenance of in-process quality at different production phases should be supported by data."	Too vague.
690	**IX. VALIDATION OF ASEPTIC PROCESSING AND STERILIZATION**	Validation of sterilization should be the subject of a separate guidance. If it remains in the Guidance, the text should be modified as indicated.
695	As noted above, a change in equipment, process, test method, or system should be evaluated through the written change control program and should trigger an evaluation of the need for revalidation or requalification. Delete "systems."	Clarification.
701	To ensure the sterility of products purporting to be sterile, sterilization, aseptic filling and closing operations must be validated	Redundant and unnecessary.

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	(211.113). Product sterility will be compromised if product elements are not sterile when they are assembled. Delete "both," "and," and "Unnecessary." Delete "The goal of even the most effective sterilization processes can be defeated if the sterilized elements of a product (the drug, the container, and the closure) are brought together under conditions that contaminate any of those elements. Similarly,."	
708	The validation of an aseptic processing operation <u>often</u> includes the use of a microbiological growth nutrient medium in place of the product. Delete "should."	Aseptic processing of bulk pharmaceutical chemicals in closed systems is the usual exception.
710	In the media fill simulation, the nutrient medium should be exposed to product contact surfaces of equipment, container closure systems, critical environments, and process manipulations to closely simulate the same exposure that the product itself will undergo. Delete "normal."	Unnecessary.
713	The sealed containers filled with the <u>medium</u> are then incubated to detect microbial contamination. Delete "media."	Correction.
714	The results <u>may be used</u> to determine the potential for a unit of drug product to become contaminated during actual operations (e.g., start-up, sterile ingredient additions, aseptic connections, filling, closing). Delete "should be interpreted."	Clarification.
721	A recommended media fill program incorporates the contamination risk factors that occur on a production line, and accurately assesses the state of process control. Media fill studies should simulate aseptic	"Worst case" is inconsistent with "simulate aseptic manufacturing operations as closely as possible."

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	manufacturing operations as closely as possible. Delete ", incorporating a worst case approach."	
737	• line speed and <u>configuration</u> Delete "configurations."	Clarification.
738	• weight checks Delete "manual."	All weight checking operations should be considered.
739	Delete "• Operator fatigue."	"Operator fatigue" is not easily measured. The normal environmental and gown monitoring programs adequately cover this aspect.
746	Media fills should not be used to justify <u>poor aseptic technique</u>. Delete "an unacceptable practice."	Clarification.
750	When a processing line is initially qualified, media fills should be repeated enough times to ensure that results are consistent and meaningful. Delete "separate."	Clarification.
753	At least three consecutive successful runs should be performed during initial line qualification. Delete "separate."	Clarification.
771	Once corrections are instituted, process simulation runs should be performed to confirm that <u>the</u> deficiencies have been corrected and the process has returned to a state of control. Delete "repeat" and "in practices and procedures."	Clarification; the deficiencies also might be equipment or system related.
773	When an investigation fails to reach well-supported, substantive conclusions as to the cause of the media fill failure, three	Clarification.

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	consecutive successful media fill runs and increased scrutiny (e.g., extra supervision, monitoring) of the production process should be implemented.	
783	In any study protocol, the duration of the run and the overall study design should adequately mimic operating conditions and cover all manipulations that are performed in the actual processing operation. Delete "worst-case."	Consistency.
795	For lyophilization operations, unsealed containers should be exposed to evacuation of the chamber in a manner that simulates the process. Delete "pressurization and partial."	Pressurization is normally not employed in lyophilization processes for pharmaceutical products.
815	Some batches are produced over multiple shifts or yield an unusually large number of units, so media fill size and duration are especially important considerations in the media fill protocol. Delete "and."	Clarification.
823	Each media fill run should evaluate a single line speed, and the speed chosen for each run during a study should be justified. Delete "individual" and "worst-case."	Clarification.
833	Media fills should be adequately representative of the conditions under which actual manufacturing operations are conducted. Delete "range of."	Clarification.
817	Some drug manufacturers have expressed concern over the possible contamination of the facility and equipment with the nutrient medium during media fill runs. Delete "media."	Correction.
859	However, if the medium is handled properly	Clarification.

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	and the media fill is promptly followed by the cleaning, sanitizing, and, where necessary, sterilization of equipment, subsequently processed products are not likely to be compromised. The use of nutrient medium in closed systems used for the production of sterile bulk pharmaceutical chemicals should be carefully evaluated relative to its potential adverse effect on subsequent operations.	There are other techniques that can be used for bulk production equipment where the use of media might be contraindicated.
873	• Incubation time should not be less than 14 days. If two temperatures are used for the incubation of the media filled units, the units should be incubated for at least 7 days at each temperature. Replace "samples" with "units."	Clarification.
879	Clear containers with otherwise identical physical properties should be used as a substitute for amber or other opaque containers used in normal production to allow visual detection of microbial growth.	Clarification.
886	Delete "Erroneously rejected units should be returned promptly for incubation with the media fill lot."	It is unclear how this might be determined.
902	In no case should more or fewer units be removed during a media fill intervention than would be cleared during a production run.	Clarification.
904	Delete "The ability of a media fill run to detect potential contamination from a given simulated activity should not be compromised by a large-scale line clearance, which can result in removal of a positive unit caused by an unrelated event or intervention. If unavoidable, appropriate study provisions should be made to compensate in such instances."	Deleted because of lack of clarity. If retained, an illustrative example should be provided.
920	The microorganisms should be identified to species level, if possible.	It may not be possible to identify microorganisms to the species level.
923	The effects on commercial products produced on the line since the last successful media fill	The product may not be a drug.

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	should also be assessed. Delete "drug."	
929	Delete "Test results should reliably and reproducibly show that the units produced by an aseptic processing operation are sterile."	A media fill is incapable of showing this. Sterility of production batches can only be implied from the results of media fill runs.
946	For any run size, recurring incidents of microbial contamination in media filled runs can be indicative of a persistent low-level contamination problem that should be investigated. Delete "intermittent."	Clarification and consistency.
956	FDA also recognizes that there are some scientific and technical limitations on how precisely and accurately validation can characterize a system of controls intended to exclude contamination. Delete "might be."	Clarification.
969	Such filters usually have a rated pore size of 0.2 micron or smaller. Delete "porosity."	Pore size is the correct term; porosity is the ratio of filter void volume to total volume.
972	The microorganisms should be small enough to both challenge the nominal pore size of the filter and simulate the smallest microorganism that may occur in production. Delete "porosity."	Pore size is the correct term; porosity is the ratio of filter void volume to total volume.
1009	Delete "The specific type of filter used in commercial production should be evaluated in filter validation studies."	Typically, filtration validation studies are conducted using disks of the same membrane material used in the commercial filter.
1017	After a filtration process is properly validated for a given product, process, and filter, it is important to ensure that filters (membrane or cartridge) used in production runs will	Clarification; see comment for line 1009.

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	perform in the same manner. Delete "identical" and "replacements."	
1027	The use of sterilizing-grade filters in series is a common practice. Delete "We recommend you consider" and "; this."	Clarification.
1042	Aseptic processing equipment should be sterilized between each processed batch, as appropriate. Delete "Sterility of aseptic processing equipment should be maintained by batch-by-batch sterilization."	Clarification.
1043	Following sterilization of equipment, containers, or closures, transportation or assembly should be performed aseptically in a manner that protects and sustains the product's sterile state. Delete "with adherence to strict aseptic methods."	Clarification.
1050	The load configuration should be documented for the validation studies and routine production. Delete "both" and "use of a specified load configuration should be documented in the batch records."	Clarification
1054	It is important to remove air from the autoclave chamber as part of a steam sterilization cycle. The insulating properties of air interfere with the ability of steam to transfer its energy to the load, achieving lower lethality than associated with saturated steam. Delete "unevacuated" and "moist heat under pressure." Delete "prevent moist heat under pressure	Any air (not just unevacuated air) can interfere with a saturated steam sterilization cycle. Air is often present, and necessary, in other types of moist heat sterilization cycles, e.g., air overpressure cycles and water spray or cascade.

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	from penetrating or heating up materials and achieving the."	
1062	Biological indicator D-values can vary widely depending on the substrate, particularly for gaseous sterilants. Delete "D-value of the" and "material to be sterilized."	Clarification.
1063	Potentially difficult to sterilize locations within the sterilizer load or equipment train (for SIP applications) should be carefully evaluated. Delete "in initial studies" and "reach."	Clarification.
1064	Delete "For example, filter installations in piping can cause a substantial pressure differential across the filter, resulting in a significant temperature drop on the downstream side. Biological indicators should be placed at appropriate downstream locations of this equipment to determine if the drop in temperature affects the thermal input at these sites."	If significant temperature drops are encountered, the sterilization cycle/method is inappropriate. Bleeders or other means to ensure uniform temperature should be employed before the cycle can be considered validatable.
1068	Validation should focus on the load areas identified as most difficult to sterilize (e.g., worst-case locations of tightly wrapped or densely packed supplies, securely fastened load articles, lengthy tubing, the sterile filter apparatus, hydrophobic filters, stopper load). Delete "Requalification and review." Delete "continue to." Delete "penetrate or heat."	Clarification.
1073	Delete "The formal program providing for regular revalidation should consider the age of the sterilizer and its past performance."	The age of the sterilizer and its past performance are addressed more appropriately in the maintenance and change control programs.
1081	It is important that these studies assess	There may not be cold

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	temperature uniformity at various locations throughout the sterilizer. Delete "to identify potential *cold spots* where there can be insufficient heat to attain sterility."	spots.
1083	These temperature distribution or *temperature mapping* studies should be conducted by placing calibrated temperature measurement devices in numerous locations throughout the chamber. Delete "heat uniformity."	It is generally not possible to measure heat uniformity. Such measurements would require the use of a calorimeter.
1117	• The microbial count and D-value of biological indicators used for validation studies should be confirmed. Delete "a" and "before a validation study."	Clarification.
1121	• If used, instruments used to determine the purity of steam should be calibrated. Delete "as appropriate."	Clarification.
1127	Equipment control should be ensured through placement of measuring devices at those control points that are most likely to rapidly detect unexpected process variability. Delete "risk-based."	Inappropriate use of the term in this context.
1144	In aseptic processing, one of the most important laboratory controls is an environmental monitoring program. Delete "the establishment of."	Clarification.
1158	Sampling should be sufficient to optimize detection of environmental contaminants at levels that might be expected in a given clean area. Delete "sizes."	Clarification.
1162	It is especially important to monitor the	The term "aseptic

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	microbiological quality of the aseptic processing during filling and closing activities. Delete "clean area to determine whether or not aseptic conditions are maintained."	conditions" is unclear in this context.
1165	Air and surface samples should be taken at locations where significant activity or product exposure occurs during production. Delete "the actual working site and at."	It is inadvisable to take samples at the "actual working site" because of the potential for introducing product contamination.
1170	If performed, critical surface sampling should take place at the conclusion of the aseptic processing operation to avoid direct contact with sterile surfaces during processing.	Clarification.
1187	Written SOPs should also address factors such as (1) frequency of sampling . . . and (7) appropriate response to deviations from alert or action levels. Delete "areas."	Clarification.
1195	Microbiological monitoring alert and action levels should be established based on the relationship of the sampled location to the operation.	Clarification.
1203	Alert and action levels for the microbiological quality of the environment should be established and each individual sample result should be evaluated for its significance by comparison to those levels. Delete "Monitoring." Delete "include both alert and action levels." Delete "alert or action."	Clarification.
1212	Trend reports should include data generated by location, shift, lot, room, operator, or other relevant parameters. Delete "search."	Clarification.
	For example, floors, walls, ceilings, and	Consistency with line 1170.

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	equipment should be tested on a regular basis. Product contact surfaces, if sampled, should be sampled only after the aseptic processing operation has concluded. Delete "product contact surfaces."	
1260	Manufacturers should be aware of a device's capabilities, and the air sampler should be evaluated for . . . disruption of unidirectional airflow. Delete "air monitoring."	Clarification.
1284	Environmental isolates often correlate with the contaminants found in a media fill or product sterility test, and the overall environmental picture provides valuable information for an investigation. Delete "testing failure."	Clarification.
1309	Incoming lots of environmental monitoring media should be tested for their ability to support microbial growth. Such testing should include positive and negative controls. Growth promotion testing should be performed on all lots of prepared media.	Clarification.
1325	We recommend the use of test methods that, upon evaluation, demonstrate increased accuracy, sensitivity, and reproducibility compared to conventional methods.	Clarification.
1331	A result outside the established levels at a given location should be investigated. Delete "specifications."	Clarification and consistency.
1339	**XI. STERILITY TESTING**	Suggest deleting this section as sterility testing is adequately addressed in other publications, e.g., USP. Serious legal implications are likely to result if this section is not deleted or substantially rewritten.

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1390	This limited sensitivity is why, for batch release purposes, it is important that an appropriate number of units are tested,[11] and that the samples uniformly represent:	There is potentially a serious legal issue here. FDA recognizes USP test methods as "official." The guidance, as written, seriously undermines this position. How many units are "appropriate"?
1424	Footnote 12 Underscoring this regulatory standard, USP 26, section <71>, states that an initial positive test is invalid only in an instance in which "microbial growth can be without a doubt ascribed to" laboratory error (as described in the monograph). Delete "XXV."	Correction. USP uses Arabic numerals for volume numbers. The current volume is 26.
1440	Deviation and sterility test positive trends should be evaluated periodically (e.g., quarterly, annually) to provide an overview of operations.	Positive sterility tests occur so infrequently that this would usually be a meaningless exercise.
1529	Any detectable disruption in power supply, however momentary, during aseptic processing is a manufacturing deviation and must be included in batch records (211.100, 211.192).	Clarification.
1546	Although few isolators form an absolute seal, very high integrity can be achieved in well-designed isolators. Delete "unit."	Clarification.
1562	Delete "Such a breach can be of serious consequence."	Redundant.
1564	Due to the potential for microbial migration through microscopic holes in gloves and the lack of a highly sensitive glove integrity test, the operator should also wear a second pair of thin gloves.	Sanitizing the inner part of the installed glove is difficult to achieve and could result in glove deterioration and irritation of the operator's hands.

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	Delete "the inner part of the installed glove should be sanitized regularly and."	
1578	Other aseptic processing isolators employ . . . Delete comma after the word employ.	Correction.
1587	As in any aseptic processing design, suitable materials should be chosen based on durability, as well as ease of cleaning and decontamination. Delete "sterilization."	Clarification.
1594	A positive air pressure differential adequate to achieve this separation should be employed and supported by qualification studies. Delete "full."	Clarification.
1615	Delete "An aseptic processing isolator should not be located in an unclassified room."	There is no scientifically valid reason that a properly designed isolator cannot be located in a controlled, but unclassified area.
1620	The ability to maintain integrity of an isolator is impacted by the design of transfer ports. Delete "and sterility."	Isolators to not have to be "sterile."
1629	Delete "Some transfer ports can have significant limitations, including marginal decontaminating capability (e.g., ultraviolet) or a design that has the potential to compromise isolation by allowing ingress of air from the surrounding room. In the latter case, localized HEPA-filtered unidirectional airflow cover in the area of such a port should be implemented."	If the transfer ports are inadequate or cannot be appropriately decontaminated, they should not be used; hence there is no need for the deleted sentences.
1646	A decontamination process should be developed that provides full exposure of all isolator surfaces to the decontaminating agent. Delete "chemical."	Clarification.
1648	For example, to facilitate contact with the decontaminant, the glove apparatus should be	Clarification.

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	fully extended with glove fingers separated during the decontamination cycle. Delete "sterilant."	
1654	A decontamination method should be developed that renders the inner surfaces of the isolator virtually free of viable microorganisms.	Clarification.
1655	Decontamination can be accomplished using a number of agents, including gases or vapors, although some agents possess limited capability to penetrate obstructed or covered surfaces. Delete "vaporized," "these" and "generally."	Clarification.
1657	The characteristics of these agents may preclude the use of statistical methods (e.g., fraction negative) to determine process lethality (Ref. 14). Delete "generally" and "reliable."	Provides needed flexibility.
1659	An appropriate, quantified BI challenge should be placed on various materials and in many locations throughout the isolator, including difficult to reach areas. Delete footnote 13 "If the various isolator materials are thoroughly evaluated during cycle development, a firm might consider placing more focus on material texture and porosity."	The footnote is overly specific. Surface texture and porosity are evaluated automatically when the various materials are inoculated.
1662	Normally, a three-log reduction can be justified depending on the application. Delete "four- to six."	There is no scientifically valid evidence that a 4- to 6-log reduction is necessary to the successful operation of an aseptic processing isolator.
1664	Delete "For example, demonstration of a four-log reduction should be sufficient for introduction of controlled, very low bioburden materials into an aseptic processing isolator, including wrapped sterile supplies	There is no scientifically valid evidence that a 4-log reduction is necessary to the successful operation of an aseptic processing isolator.

Note: Additions to text are underlined.

Line Number	Suggested Change	Rationale
	that are briefly exposed to the surrounding cleanroom environment."	
1668	The distribution of the decontaminating agent should also be evaluated concurrent with these studies (Ref. 15). Delete "uniform" and "defined concentration of."	Clarification.
1675	When an isolator is used for multiple days between decontamination cycles, the frequency adopted should be justified. Delete "include a built-in safety margin and" and "well."	It is unlikely that a "built-in safety margin" can be determined.
1683	Breaches of integrity should be investigated and the impact of the breach on any product that may have been implicated should be evaluated. Delete "impacted by the breach rejected."	It is unnecessary to automatically reject product.
1688	To ensure sterility of product contact surfaces from the start of each operation, the entire path of the sterile processing stream should be sterilized. Delete "liquid."	The product may not be a liquid, e.g., it could be a sterile powder.
1698	An environmental monitoring program should be established to ensure microbiological quality of air, surfaces, and gloves (or half-suits) as well as particle levels, as necessary, remain within established levels within the isolator. Delete "appropriate," "that," "routinely" and "acceptable."	The term "acceptable" is undefined and particulate level monitoring may not be appropriate in some instances, e.g., during powder fills.
1705	Cleanroom apparel considerations are generally reduced in an isolator operation. Delete "while" and "requirements." Delete ", the contamination risk contributed by manual factors should not be overlooked."	Clarification.

 Note: Additions to text are underlined.

Line Number	Suggested Change	Rationale
1706	Delete "Isolation processes generally include periodic or even frequent use of one or more gloves for aseptic manipulations and handling of material transfers into and out of the isolator."	Redundant.
1708	However, one should be aware that locations on gloves, sleeves, or half suits can be among the more difficult to reach places during surface decontamination, and glove integrity defects may not be promptly detected. Delete "sterilization."	Clarification.
1738	Throughout this operation, sterile air is used, for example, to form the parison and inflate it prior to filling. Delete "-."	Correction.
1743	BFS machinery and its surrounding barriers should be designed to prevent extraneous contamination. Delete "potential for."	Clarification.
1744	As with any aseptic processing operation, it is critical that product contact surfaces be sterile.	Clarification.
1745	A validated cycle should be used to sterilize the equipment path through which the product is conveyed. Delete "steam-in-place."	Other types of sterilization may be appropriate.
1746	Delete "In addition, any other surface with the potential to contaminate the sterile product should be sterile.	The sentence is too broad to be meaningful.
1727	The polymer material chosen should be pharmaceutical grade, safe, pure, and pass appropriate criteria (Ref. 17) for plastics. Delete "plastic."	Clarification.
1797	Samples should be taken according to a comprehensive sampling plan that provides data representative of the entire filing operation.	Clarification.

 Note: Additions to text are underlined.

Line Number	Suggested Change	Rationale
	Delete "per."	
1802	It is critical that the operation be designed and set-up to uniformly manufacture integral units. Delete "leak-proof."	No unit is "leak proof."
1805	Significant defects due to heat or mechanical problems, such as wall thickness, container or closure interface deficiencies, poorly formed closures, or other deviations should be investigated in accord with §§ 211.100 and 211.192. Delete "mold."	Correction.
1812	The purpose of this appendix is to supplement the guidance provided in this document . . . because it is impossible to filter sterilize the final drug product. Delete "sterilyze."	Correction.
1824	In other instances, the final drug product cannot be filter sterilized, and, therefore, each component in the formulation would be rendered sterile and mixed aseptically. Delete "sterilyze."	Correction.
1880	4. Ljungqvist, B., and Reinmüller, B., *Clean Room Design: Minimizing Contamination Through Proper Design;* Interpharm Press, 1997. Delete "Reinmuller."	Correction.
1899	13. Pharmacopeial Forum, July-August 1980, p. 354, "Commentary on the Sterility Tests and Sterilization Chapters of the U.S. Pharmacopeia," Aubrey S. Outschoorn, Sr. Scientist, U.S.P. Drug Standards Division. Delete "Pharmacopoeial" and "Pharmacopoeia."	Correction.

 Note: Additions to text are underlined.

Line Number	Suggested Change	Rationale
1909	17. United States Pharmacopeia Delete "Pharmacopoeia."	Correction.
2022	Delete "Laminar flow- An airflow moving in a single direction and in parallel layers at constant velocity from the beginning to the end of a straight line vector."	This term is not used in the document, so it is unneeded in the Glossary.

Note: Additions to text are underlined.