Aventis Behring

November 3, 2003

Division of Dockets Management (HFA-305)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane; Room 1061
Rockville, MD 20857

Docket No. 2003D-0382

Re: Draft Guidance for Industry on ``Sterile Drug Products Produced by Aseptic Processing"

To Whom It May Concern:

Aventis Behring is pleased to provide comments on FDA's recently issued draft guidance entitled, "Sterile Drug Products Produced by Aseptic Processing," which was announced in the Federal Register, Volume 68, Number 172, page 52782-52783, on September 5, 2003.

Aventis Behring is a manufacturer of plasma derived protein therapeutic products with manufacturing operations in the United States and Europe. The information provided herein represents a consensus of comments provided by these manufacturing sites and our corporate quality assurance department. The enclosed table contains 94 comments and/or suggestions for alternative wording of portions of the guidance text. We hope that you find our comments useful.

We appreciate the opportunity to provide feedback to FDA on this important guidance document and we wish to provide encouragement to FDA on its drug quality initiative.

Sincerely,

Michael Gross
Vice President, Worldwide Compliance

2003D-0382 C22

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AVENTIS BEHRING COMMENTS

Guidance For Industry Draft Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing - Current Good Manufacturing Practice

Comment Number	Line Number	Current Draft Text	Recommended Revision	Comment/Rationale
1.	73-74	"Terminal sterilization usually involves filling and sealing product containers under high-quality environmental conditions."		The term "high-quality environmental conditions" should be defined.
2.	76-77	"In most cases, the product, container, and closure have low bioburden, but they are not sterile." .		The term "low bioburden" should be defined.
3.	81-83	"Because there is no process to sterilize the product in its final container, it is critical that containers be filled and sealed in an extremely high-quality environment."	"Because there is no process to sterilize the product in its final container, it is critical that containers be filled and sealed in a high-quality environment."	Comment: The term "extremely high-quality environment" should be defined or eliminated.
4.	88-89	"Each of these aseptic manufacturing processes requires thorough validation and control."	"Each of these aseptic manufacturing processes requires validation and control."	The phrase "thorough validation" implies that there are two levels of validation. For this reason it is suggested that the word "thorough" be deleted.

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5.	114-115	"In such cases, a manufacturer can explore the option of adding adjunct processing steps to increase the level of sterility confidence." .		The terms "adjunct processing steps" and "sterility confidence" should be defined; or notwithstanding, delete them since it is not likely that and SAL of 10^-3 can be exceeded even if "adjunct processing steps are added".
6.	134-136	"Critical areas and support areas of the aseptic processing operation should be classified and supported by microbiological and particle data obtained during qualification studies."	"Critical areas and supporting clean areas of the aseptic processing operation should be classified and supported by microbiological and particle data obtained during qualification studies."	The phrase "support areas" is very broad and could be interpreted to include ingredient storage areas or other widely varying areas beyond the intention of this guidance document. In light of language used later on, it is suggested that "support areas" be changed to "supporting clean areas", so that the definition and specifications of "clean areas" provided later in the document are clearly associated with this thought.
7.	139	"The following table summarizes clean area air classifications (Ref. 1)"		Comment: Table 1-Air Classifications, references ISO 14644-1, however ISO 14644-1 does not contain the microbiological limits cited in the table. The bracket

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				term "(Ref. 1)" should deleted, because adequate reference to ISO 14644-1 is given in footnote b (Lines 147-148).
8.	152 (footnote e)	Samples from Class 100 (ISO 5) environments should normally yield no microbiological contaminants."	Delete footnote	In Table 1 the value of "1" is given. This does not correspond to the term "normally yield no microbiological contaminants
9.	173-175	: "...particle count of no more than 3520 in a size range of 0.5 micron and larger when counted at representative locations normally not more than one foot away from the work site,..."		The guidance should define the term "work site" to avoid misunderstandings.
10.	183-185	"Measurements to confirm air cleanliness in aseptic processing zones should be taken with the particle counting probe oriented in the direction of oncoming airflow and at the sites where there is most potential risk to the exposed sterilized product and container-closures."	"Measurements to confirm air cleanliness in aseptic processing areas should be taken with the particle counting probe oriented in the direction of oncoming airflow and at the sites where there is most potential risk to the exposed sterilized product and container-closures."	The word "zones" is not defined ar is used alternately with "area". For consistency, it is suggested that the word "zone" be replaced by "area" throughout
11.	186-188	Change from: "Nonviable particle monitoring with a	Change to: "Nonviable particle monitoring with a	The guidance document provides no data justifying the statement that the

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		remote counting system is generally less invasive than the use of portable particle counting units and provides the most comprehensive data."	remote counting system is generally less invasive than the use of portable particle counting units and is recommended for this reason."	remote counting system provides more comprehensive data than the portable particle counting units. And this is not necessarily the case, as many portable units could be put into place and operated for the same time period that the remote units are in operation. In addition, the portable units provide more flexibility as to location and therefore can provide more coverage of different areas in a clean or critical area, which meets one definition of "comprehensive." Therefore it is suggested that the statement "and provides the most comprehensive data" be deleted. However, the point that the remote unit is less invasive does give a rationale for a general recommendation, and therefore it is suggested that the phrase "and is recommended for this reason" be added.

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12.	196-198	"Air in critical areas should be supplied at the point of use as HEPA-filtered laminar flow air at a velocity sufficient to sweep particles away form the filling/closing area and maintain unidirectional airflow during operations."	"Air in critical areas should be supplied at the point of use as HEPA-filtered unidirectional flow air at a velocity sufficient to sweep particles away form the filling/closing area and maintain unidirectional airflow during operations."	The term "laminar" should be replaced by the term "unidirectional.", because laminar airflow is not really achievable. Further the term "a velocity sufficient to sweep particles away" should be described more exactly.
13.	199-201	"Air in critical areas should be supplied at the point of use as HEPA-filtered laminar flow air at a velocity sufficient to sweep particles away from the filling/closing area and maintain unidirectional airflow during operations."	"Air in critical areas should be supplied at the working site as HEPA-filtered laminar flow air at a velocity sufficient to sweep particles away from the filling/closing area and maintain unidirectional airflow during operations."	The phrase "point of use" has been a contentious issue in the past, as this may be considered to be at the HEPA face. To clarify that the "point of use" is at the "working height" or "work site" it is suggested that the change be made, which is consistent with the language on page 5 line 178.
14.	222-224	Many support areas function as zones in which nonsterile components, formulated products, in-process materials, equipment, and container/closures are prepared, held, or transferred.".	"Many support areas function as areas in which nonsterile components, formulated products, in-process materials, equipment, and container/closures are prepared, held, or transferred."	The word "zones" is not defined and is used alternately with "area". For consistency, it is suggested that the word "zone" be replaced by "area" throughout

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15.	page 6, footnote 4	"A velocity from 0.45 to 0.51 meters/second (90 to 100 feet per minute) is generally established, with a range of plus or minus 20 percent around the setpoint. Higher velocities may be appropriate in operations generating high levels of particulates."	"A velocity from 0.45 meters/second (90 feet per minute) is generally established, with a range of plus or minus 20 percent around the set-point. Higher velocities may be appropriate in operations generating high levels of particulates."	The original statement provides for a range (+/- 20%) around a range 0.45-0.51 with an allowance for higher velocities. It would be similar to providing a target, a range and then the allowance for higher velocities if needed, and this is the change suggested. In addition the suggested criteria provides for harmonization with the European GMPs. Harmonization of requirements at the earliest possible moment (such as within this guidance) is desirable to more quickly reach to overall harmonization goals.
16.	229-230	: "Depending on the operation, manufacturers can also classify this area as Class 1,000 (ISO 6) or maintain the entire aseptic filling room at Class 100 (ISO 5)."	delete	The category ISO 6 (Class 1,000) i not common within pharmaceutical manufacturing and should be deleted in the guidance.
17.	238-241	"For example, a positive pressure differential of at least 12.5 Pascals (Pa) should be maintained at the interface between classified and		Pressure differentials of 12.5 Pascals should only be defined between rooms of different classification, not for all rooms

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		unclassified areas. This same overpressure should be maintained between the aseptic processing room and adjacent rooms (with doors closed)."		adjacent to an aseptic processing room (if these rooms are of the same classification).
18.	242-243	"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."	"For example, a positive pressure differential of at least 10 Pascals (Pa)[5] should be maintained at the interface between classified and unclassified areas."	The suggested criteria provides for harmonization with the European GMPs. Harmonization of requirements at the earliest possible moment (such as within this guidance) is desirable to more quickly reach to overall harmonization goals. In this case, the footnote on page 7 should also be changed to read " Equal to 0.041 inches of water gauge."
19.	266-268	"A compressed gas should be of appropriate purity (e.g., free from oil and water vapor) and its microbiological and particle quality should be equal to or better than air in the environment into which the gas is introduced."	"A compressed gas should be of appropriate purity (e.g., free from oil [< x%] and water vapor[< x %]) and its microbiological and particle quality should be equal to or better than air in the environment into which the gas is introduced."	Limits need to be provided to prevent ever more costly methodology adoption.

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20.	272-273	"Sterilized holding tanks and any contained liquids should be held under continuous overpressure to prevent microbial contamination."	Delete or revise to, "Sterilized holding tanks and any contained liquids should be held under continuous overpressure or the tanks should be post use integrity checked to prevent microbial contamination, if there is no subsequent sterilizing filtration."	During some operations, overpressure is not feasible (e.g., transfer of product between vessels). The emphasis should be put on confirmation of vessel integrity.
21.	287-289	"Therefore, leak tests should be performed at suitable time intervals for HEPA filters in the aseptic processing facility. For example, such testing should be performed twice a year for the aseptic processing room."		The minimum frequencies for testing should be based on ISO recommendations (ISO 14644-2).
22.	283-284	"Filters also should be integrity tested upon installation and periodically thereafter (e.g., including at end of use)."	"Filters also should be integrity tested upon installation, at end of use and after activities that might damage the filter. In no case should the time period between integrity tests extend beyond one year."	If the maximum time period between tests is one year, periodic testing of air or gas filters is not necessary. After accidental bumping or other mistreatment the filters may need retesting to assure integrity.
23.	297-298	Lines 297-298: "Dioctylphthalate (DOP) and Poly-alpha-olefin (PAO) are examples of appropriate leak testing aerosols."		Di-Ethyl-Hexyl-Sebacate (DEHS) should be added to the list of appropriate leak testing aerosols, as this is also commonly used.

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24.	333-342	"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., 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."	"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., 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. Periodic velocity monitoring can provide useful data for the area in which aseptic processing is performed, and should be performed at least quarterly. 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."	There is no definition as to how much more frequently airflow velocities should be measured than the required semi-annual leak testing. Inasmuch as this is an extraordinary event in the critical area, it should be done at the minimal necessary frequency, and quarterly is suggested. In addition, it is suggested that the word "regular" be replaced with "periodic" for consistency with the previous sentence, and to change "on the clean area" to "for the area" as the topic is the critical area. This use of clean in this sense could be confused with "clean area" which has separate requirements and lin. than the "critical area."

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25.	348	"...clean area are essential to achieving high assurance of sterilty (Ref. 4)."	"...clean area are essential to achieving high assurance of sterility (Ref. 4)."	The word "sterilty" is misspelled.
26.	355	"sterilty"	"sterility"	Spelling correction.
27.	380-382	"Facility design should ensure that the area between a filling line and the lyophilizer and the transport and loading procedures provide Class 100 (ISO 5) protection."	"Facility design should ensure that the area between a filling line and the lyophilizer and the transport and loading procedures provide Class 100 (ISO 5) protection. Alternate methods of providing Class 100 protection for partially closed sterile products during transport between the filling area and the lyophilizer may be used, such as transport trolleys with integral HEPA filtered air supply."	The requirement is for clean (Class 100) conditions between the filling area and lyophilizer, and the guidance should specify the what (the conditions) and not the how (area cleanliness). The additional sentence provides allowance for alternate means to same goal.
28. **	411-414	"With rare exceptions, drains are not considered appropriate for classified areas of the aseptic processing facility."	"With rare exceptions, drains are not considered appropriate for critical areas."	Since many aseptic processing facilities include the washing of containers, and the area in which the containers are washed is classified, and the waste water must be

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				disposed of, the sentence as written is too restrictive. On container washers the drain may be off the floor, with an air-break and contained within the machine, but it is a drain by any other name. The sentence has been adjusted appropriately to limit the restriction to critical areas, not all classified areas.
29.	460-462	Rapid movements can create unacceptable turbulence in the critical zone. Such movements disrupt the sterile field, presenting a challenge beyond intended cleanroom design and control parameters."	"Rapid movements can create unacceptable turbulence in the critical area. Such movements disrupt the airflow laminarity, presenting a challenge beyond intended cleanroom design and control parameters."	The term "critical zone" is apparently used as a synonym to "critical area" as "clean zone" is cross-referenced to "clean area." As such, for consistency and clarity, it is suggested that all such references be changed from "critical zone" to "critical area." Furthermore, the aseptic processing area is not a sterile area by definition; it has not been sterilized. The term "sterile field" is a misnomer that implies sterility of the area and should be changed for clarity. Therefore it is suggested that "sterile field be replaced with "airflow laminarity."

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30.	468-469	"Personnel should not disrupt the path of unidirectional flow air in the aseptic processing zone."	"Personnel should not disrupt the path of unidirectional flow air in the aseptic processing area."	The word "zones" is not defined and is used alternately with "area". For consistency, it is suggested that the word "zone" be replaced by "area" throughout.
31.	476-477	"Also, an operator should refrain from speaking when in direct proximity to an aseptic processing line."	"Also, an operator should refrain from speaking when within the critical area of an aseptic processing line."	It is unclear whether "direct proximity" means in the Class 100 laminar flow area or next to it, but outside the Critical Area. If it means the later, the statement is too general. For instance, outside the Critical Area but next to it could mean a person standing next to an isolator. In this instance, the talking prohibition is too extreme. Therefore it is suggested that the phrase "in direct proximity to an aseptic processing line" be changed to "within the critical area of an aseptic processing line."
32.	487-490	"Gowns should be sterile and nonshedding and should cover the skin and hair (face-masks, hoods,	"Gowns should be sterilized and nonshedding and should cover the skin and hair (face-masks, hoods,	Once a gown is donned, it cannot be considered sterile. Elsewhere in the guidance, for instance, in line 552

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		beard/moustache covers, protective goggles, elastic gloves, cleanroom boots, and shoe overcovers are examples of common elements of gowns)."	beard/moustache covers, protective goggles, elastic gloves, cleanroom boots, and shoe overcovers are examples of common elements of gowns)."	where containers and closures are discussed, the term sterilized is used. For consistency and clarity, it is suggested that the term "sterilized" be used in place of "sterile" in this instance.
33.	588-589	Endotoxin "challange studies should be performed with a reconstituted endotoxin solution applied directly onto the surface being tested and air-dried.	Endotoxin "challenge studies may be performed with a reconstituted endotoxin solution applied directly onto the surface being tested and air-dried." The use of precoated vials may also be acceptable.	The mention of a specific procedure can discredit alternative equivalent reliable procedures and/or discourage technological advancements.
34.	629-630	"A container closure system that permits penetration of air, or microorganisms, is unsuitable for a sterile product."	The term "air, or" should be deleted	Penetration by air and other gases can occur without compromising product sterility, e.g. by diffusing through elastomeric closures, or through sterilization bag membranes..
35.	634-636	"The finished dosage form manufacturer is responsible for the review and approval of the contractor's validation protocol and final validation report."	"The finished dosage form manufacturer is responsible to assure that the contractor's validation protocol and final validation report are in place and acceptable."	Normally, it would be expected that "approval" of the protocol and report be signatures by the manufacturer on the protocol and report. Since the contractor may well be providing these items for several manufacturers now, and more in the future, the concept that each

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				future, the concept that each manufacturer is to sign the protocol (in advance of execution) and sign the report is clearly untenable. The manufacturer need only assure th the protocol and report are in place and appropriate, which may be done through audit, through signing the documents and other methods. The suggested changes reflect this
36.	660-661	"Endotoxin control should be exercised for all product contact surfaces both prior to and after sterile filtration."	This sentence should be deleted.	The risk of contaminating product is prevented by product tests, equipment qualification, and validation of cleaning or either dry heat processes.. Endotoxin control for product contact surfaces prior and after every routine sterile filtration of no real benefit.
37.	668-669	"Processes that are designed to achieve depyrogenation should demonstrate a 3-log reduction of endotoxin."		This approach is only applicable, if the endotoxin concentration before the depyrogenation is known (e.g. for spiked "challenge vials" during validation). As the starting concentration is not consistent, the method has to be described more in detail (e.g., use of average endotoxin concentrations of the

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				positive controls as starting point). Another possibility is to define the acceptance criteria as "< 1 Endotoxin Unit".
38.	667-668	"Equipment should be dried following cleaning."	"Following cleaning, equipment should be handled in such a manner as to prevent contamination otherwise affect the safety, purity or potency of the following product manufactured in the equipment(e.g. drying or setting time limits between cleaning and use)."	In many instances, a new batch is processed by the equipment quickly following cleaning. For intermediate purification processes, using wet equipment will not affect the safety, purity or potency of the intermediate materials; drying provides no benefit. The purpose of drying would appear to be to limit the opportunities for microorganism growth. This would equally be met by setting time limits between cleaning and use, as well as protecting the clean equipment. The suggested wording provides the necessary flexibility as well as specifies "what" is needed, rather than requiring the "how."
39.	684-685	"Sterilizing-grade filters should generally be replaced following each manufactured lot."		The term "generally" can be misinterpreted. Specific guidance would be helpful.

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40.	689-690	"Maintenance of in-process quality at different production phases should be supported by data."	"The time limits set for the various production phases should be supported with drug product quality data."	The suggested wording is to make it clear that it is the "time limits", which are the topic of this section, that are to be supported by the data demonstrating appropriate levels of drug product quality at the various production phases.
41.	701-702	"To ensure the sterility of products purporting to be sterile, both sterilization and aseptic filling and closing operations must be adequately validated (211.113)."	"To ensure the sterility of products purporting to be sterile, both sterilization and aseptic filling and closing operations must be validated (211.113)."	The phrase "adequately validated" implies that there are two levels of validation, regular validation and the "adequate validation." Nowhere in US GMP or FDA guidance is the difference explained. The word "adequately" provides no more guidance as to what is required for validation of aseptic processes than does the single word "validation." In addition, the GMP citation given (211.113) uses "validation," not "adequately validated." For this reason it is suggested that the word "adequately" be deleted.
42.	722-724; 739	"Media fill studies should simulate aseptic manufacturing operations as closely as possible, incorporating a	Media fill studies should simulate aseptic manufacturing operations as closely as possible, incorporating a worst-case	It is generally not possible to artificially simulate fatigue. The term in line 739 should be deleted.

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		worst-case approach. The media fill program should address applicable issues such as:"; "operator fatigue"	approach.	
43.	757-758	"Media fills should not be used to justify an unacceptable practice."	delete	The phrase "unaccepted practice" a vague term and is not defined within this document. People will differ as to what unaccepted practices are. Since validation, such as validation of aseptic processes through media fills, are a justification of the process, this statement is in fact contradictory. If there are specific concerns, or even examples, of practices that are objectionable or unacceptable, it is suggested that these be included here, rather than using this broad and vague language.
44.	773-778	" Any changes or events that have the potential to affect the ability of the aseptic process to exclude contamination from the sterilized product should be assessed through additional media fills. For example, facility and equipment modifications, line configuration changes,	" Any changes or events that have the potential to affect the ability of the aseptic process to exclude contamination from the sterilized product should be assessed through additional media fills. For example, facility and equipment modifications, line configuration changes, significant changes in personnel,	The outcome of the events listed in this sentence is "revalidation of the system." This is more rigorous than an additional media fill run, and is described on this page as "separate media fills should be repeated enough times to ensure that results are consistent and meaningful."

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		significant changes in personnel, anomalies in environmental testing results, container closure system changes or, end product sterility testing showing contaminated products may be cause for revalidation of the system."	anomalies in environmental testing results, container closure system changes or, end product sterility testing showing contaminated products may be cause for additional media fills, or even revalidation of the system."	Making a requirement for revalidation due to the undefined "anomalies in environmental testing results" is overkill and unnecessary. The "additional media fills" stated the first sentence above provides the flexibility and range of approaches to provide an appropriate level of media fills for the concerns noted, while the re-validation of the line is a much more intensive effort. It is suggested that the second sentence be reworded to include as an option "additional media fills" as noted above to reflect the broader list of options.
45.	780-782	"Where data from a media fill indicate the process may not be in control, a comprehensive documented investigation should be conducted to determine the origin of the contamination and the scope of the problem."	"Where data from a media fill indicate the process may not be in control, an investigation should be conducted to determine the origin of the contamination and the scope of the problem."	The phrase "comprehensive documented investigation" implies that there are two levels of investigations, regular investigations and the more rigorous and in-depth "comprehensive investigations." Nowhere in US GMP or FDA guidance is the difference explained. The word "comprehensive" provides no more guidance as to what is required for investigations than does

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				the single word "investigation." For this reason it is suggested that the word "comprehensive" be deleted. In addition, the GMP requirement is that investigations must be in documented form. Specifying "documented" in one case but not in the others implies that some investigations may not need to be documented. Therefore it is suggested that the word "documented" also be deleted.
46.	817-819	"For operations with production sizes under 5,000, the number of media filled units should equal the maximum batch size made on the processing line (Ref. 8)."	"For operations with production sizes under 5,000, the number of media filled units should be equal to or greater than the maximum batch size made on the processing line (Ref. 8)."	The suggested wording provides for harmonization with the current practice vast majority of industry, as well as harmonization with the European GMPs. Harmonization of requirements at the earliest possible moment (such as within this guidance) is desirable to more quickly reach to overall harmonization goals.
47.	865-869	"The production process should be accurately simulated using media and conditions that optimize detection of any microbiological	The production process should be accurately simulated using media and conditions that optimize detection of any microbiological contamination. Each unit	The word "appropriate" is not as specific as "sufficient" and does not as clearly denote that there must be enough volume of media for the

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		contamination. Each unit should be filled with an appropriate quantity and type of microbial growth medium to contact the inner container closure surfaces (when the unit is inverted or thoroughly swirled) and permit visual detection of microbial growth."	should be filled with a sufficient quantity and type of microbial growth medium to assure contact of all inner container closure surfaces (when the unit is inverted or swirled) and permit visual detection of microbial growth."	purpose of coating the interior of the container and closure surfaces. In addition, including the word "all" clearly defines the requirement. Swirling the vial may not coat all surfaces, but inserting the word all makes it clear that all surfaces are to be coated, whatever the methodology used. Finally, the word "thoroughly" does not have a clear operational definition, and provides no utility once the word "all" is inserted to provide the operational definition.
48.	877-878	"Each media-filled unit should be examined for contamination by personnel with appropriate education, training, and experience in microbiological techniques."	"Each media-filled unit should be examined for contamination by personnel with appropriate education and training in microbiological techniques."	To have experience in microbiological techniques is not mandatory necessary for the examination of media-filled units. This term should be deleted.
49.	897-898 and footnote 9	"If written procedures and batch documentation are adequate, these intervention units do not need to be incubated during media fills.[9]"; "To assess contamination risk	"If written procedures and batch documentation are adequate, these intervention units do not need to be incubated during media fills.	The footnote should be removed, because obtained data would have no value, as it is not representative of risks for the actual product

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		during initial aseptic setup (before fill), valuable information can be obtained by incubating all such unites that may be normally removed."		
50.	904-906	"Any decision to exclude such incubated units (i.e., nonintegral) from the final run tally should be fully justified and the deviation explained in the media fill report."	"Any decision to exclude such incubated units (i.e., nonintegral) from the final run tally should be justified and the deviation explained in the media fill report."	The phrase "fully justified" implies that there are two levels of justification, regular justification and the more rigorous "fully justified." Nowhere in US GMP or FDA guidance is the difference explained. The word "fully" provides no more guidance as to what is required for justification at this point than does the single word "justified." For this reason it is suggested that the w "fully" be deleted.
51.	906-908	"If a correlation emerges between difficult to detect damage and microbial contamination, a thorough investigation should be conducted to determine its cause (see Section VI.B)."	"If a correlation emerges between difficult to detect damage and microbial contamination, an investigation should be conducted to determine its cause (see Section VI.B).	The phrase "thorough investigation" implies that there are two levels of investigation, regular investigation and the more rigorous and in-depth "thorough investigation." Nowhere in US GMP or FDA guidance is the difference explained. The word "thorough" provides no more guidance as to what is required for

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				investigations than does the single word "investigation." For this reason it is suggested that the word "thorough" be deleted.
52.	916-917	"Video recording of media fill has been found to be useful in identifying personnel practices that could negatively impact the aseptic process."	delete	This sentence could indicate that video recording is mandatory. The identification of negative impact on the aseptic process could also be covered by other methods (e.g., manual observation and assessment by experienced personnel).
53.	936-937	"Any contaminated unit should be considered as objectionable and fully investigated. The microorganisms should be identified to species level."	"Contaminated units should be considered as objectionable and investigated. In the event of a systemic failure, randomly selected container should be sampled for microorganism identification. If fewer than 20 container are contaminated, the microorganisms of each container should be identified to species level."	The phrase "fully investigated" implies that there are two levels of investigations, regular investigations and the more rigorous and in-depth "full investigation." Nowhere in US GMP or FDA guidance is the difference explained. The word "fully" provides no more guidance as to what is required for investigations than does the single word "investigated." For this reason it is suggested that the word "fully" be deleted. The implication of the first sentence is that every contaminated

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				vial will be speciated. However, in the event, however unlikely, of a system failure where many containers are contaminated, identification of microorganisms in each and every container is a waste of resources better used to investigate and correct the underlying problem.
54.	937-939	"In the case of a media fill failure, a comprehensive investigation should be conducted, surveying all possible causes of the contamination."	"In the case of a media fill failure, an investigation should be conducted, surveying all possible causes of the contamination."	The phrase "comprehensive investigation" implies that there are two levels of investigations, regular investigations and the more rigorous and in-depth "comprehensive investigations." Nowhere in US GMP or FDA guidance is the difference explained. The word "comprehensive" provides no more guidance as to what is required for investigations than does the single word "investigation." For this reason it is suggested that the word "comprehensive" be deleted.

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55.	949-961	"Recommended criteria for assessing state of aseptic line control are as follows: • When filling fewer than 5000 units, no contaminated units should be detected. • When filling from 5,000 to 10,000 units: -- 1 contaminated unit should result in an investigation, including consideration of a repeat media fill. -- 2 contaminated units are considered cause for revalidation, following investigation. • When filling more than 10,000 units: -- 1 contaminated unit should result in an investigation. ■ 2 contaminated units are considered cause for	"The target should be zero contaminated units, but a contamination rate less than 0.1% with 95% confidence limits is acceptable. The manufacturer should establish alert and action limits based upon historical data of the firm, and any contamination should be investigated. In particular: When filling less than 4750 contains, no contaminated units should be detected. When filling from 4750 - 6300 units, 1 contaminated unit should result in an investigation, including consideration of a repeat media fill. 2 contaminated units are considered cause for revalidation, following investigation. and so forth for larger fills."	The suggested criteria provides for harmonization with the current practice vast majority of industry, as well as harmonization with the European GMPs. Harmonization c requirements at the earliest possible moment (such as within this guidance) is desirable to more quickly reach to overall harmonization goals.

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		revalidation, following investigation. "		
56.	1008-1010	"When sufficiently justified, the effects of the product formulation on the membrane's integrity can be assessed using an appropriate alternate method." .	"When justified, the effects of the product formulation on the membrane's integrity can be assessed using an appropriate alternate method"	The phrase "sufficiently justified" implies that there are two levels of justification, regular justification an the more rigorous "sufficiently justified." Nowhere in US GMP or FDA guidance is the difference explained. The word "sufficiently" provides no more guidance as to what is required for justification at this point than does the single word "justified." For this reason it is suggested that the word "sufficiently" be deleted.
57.	1023-1028	"Filter validation experiments, including microbial challenges, need not be conducted in the actual manufacturing areas. However, it is essential that laboratory experiments simulate actual production conditions. The specific type of filter used in commercial production should be evaluated in filter validation studies. When the more complex filter validation tests	"Filter validation studies, including microbial challenges, need not be conducted in the actual manufacturing areas. However, it is essential that laboratory studies simulate actual production conditions. The specific type of filter used in commercial production should be evaluated in filter validation studies. When the more complex filter validation studies go beyond the capabilities of the filter user, tests are	There are three different words us to describe the validation activities in a short paragraph, and it is not clear if these are all different activities with different ends in mind, or merely different words to describe the same activity. Since they do not appear to be defined separately, it is suggested that "studies," "experiments" and "tests" in this context be all changed to a

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		go beyond the capabilities of the filter user, tests are often conducted by outside laboratories or by filter manufacturers."	often conducted by outside laboratories or by filter manufacturers."	consistent term, such as "studies" chosen above, for ease of reading and comprehension.
58.	1117-1118	"The microbial count and D-value of a biological indicator should be confirmed before a validation study."		The term "should be confirmed" in relation to D-values should be described more exactly. Normally the supplier certifies the microbial count and D-value. If the D-value of a bioindicator must be confirmed before use, specific testing devices are needed (this is not a current GMP requirement).
59.	1152-1154	"The monitoring program should cover all production shifts and include air, floors, walls, and equipment surfaces, including the critical surfaces that come in contact with the product, container, and closures."	delete	Critical surface monitoring is not advisable because these surfaces are sterilized using validated processes. Further the monitoring of floors gives no meaningful information about aseptic processing. The purpose of environmental monitoring should be to assess the conditions around the critical filling operation and adjacent support areas.

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60.	1158-1160	"Sampling size should be sufficient to optimize detection of environmental contaminants at levels that might be expected in a given clean area."	"Sampling size should be sufficient to optimize detection of environmental contaminants at levels that might be expected in a given clean area. For example a sampling size of 25 cm^2 for class A / class 100 / ISO 5 areas would be considered as typical." Add example: "Sampling size should be sufficient to optimize detection of environmental contaminants at levels that might be expected in a given clean area. For example a sampling size of 25 cm^2 for class A / class 100 / ISO 5 areas would be typical and sufficient."	The wording "sufficient to optimize detection" is vague and should be explained further or defined.
61.	1170-1171	"Critical surface sampling should be performed at the conclusion of the aseptic processing operation to avoid direct contact with sterile surfaces during processing."	delete	Critical surface monitoring is not advisable because these surfaces are sterilized using validated processes. Further, the monitoring of floors gives no meaningful information about aseptic processing. The purpose of environmental monitoring should be to assess the conditions around the critical filling operation and adjacent support areas.

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62.	1178-1180	"Because of the likelihood of false negatives, consecutive growth results are only one type of adverse trend. Increased incidence of contamination over a given period is an equal or more significant trend to be tracked."		The matter and its implementation of the term "Increased incidence of contamination over a given period" should be described.
63.	1189	"Critical surfaces that come in contact with the sterile product should be sterile."	Delete	This sentence is in the environmental monitoring portion of the guidance. It provides no guidance for environmental monitoring, and it is suggested that it be eliminated from this section to prevent confusion. There is no environmental monitoring that can show or prove sterility, and it is not normally feasible to sample the product contact surfaces in an aseptic filling area, which are the interior of a vessel, the hoses, the vials and filling needles.
64.	1197-1199	"One should also consider environmental monitoring data from historical databases, media fills,	"One should also consider environmental monitoring data from historical databases, media fills, clean room qualification and	Alert limits should be based on historical data and action limits could be kept at guideline limits

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		cleanroom qualification and sanitization studies, in developing monitoring levels"	sanitization studies, in developing monitoring alert levels."	corresponding to a defined clean room classification. Violation of alert limits would initiate an evaluation of potential risks to the sterility assurance and increase the alertness of the responsible departments for processes in the aseptic filling area. This two limit approach is practical when the difference between alert and guideline limit is too narrow to have a third statistically significant limit, the action limit.
65.	1205	"Averaging of results can mask unacceptable localized conditions."	delete	As averaging results is a recommendation of EU GMP Annex 1.
66.	1212-1215	"Trend reports should include data generated by location, shift, lot, room, operator, or other search parameters. The quality control unit should be responsible for producing specialized data reports (e.g., a search on a particular isolate over a year period) with the goal of investigating results beyond established levels and identifying		This requirement means a radical new approach. The described trending criteria and frequency suggests the use of a high-level trending program. Therefore, the specificity of reporting requirements should be reduced.

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		any appropriate follow-up actions."		
67.	1225-1227	"The effectiveness of these sanitization procedures should be measured by their ability to ensure that potential contaminants are adequately removed from surfaces (i.e., via obtaining samples before and after sanitization)."	delete	Samples before sanitization are normally not taken.
68.	1226-1230	"Monitoring the microbiological quality of the environment should include both alert and action levels. Each individual sample result should be evaluated for its significance by comparison to the alert or action levels. Averaging of results can mask unacceptable localized conditions. A result at the alert level urges attention to the approaching action conditions. A result at the action level should prompt a more thorough investigation."	"Monitoring the microbiological quality of the environment should include both alert and action levels. Each individual sample result should be evaluated for its significance by comparison to the alert or action levels. Averaging of results can mask unacceptable localized conditions. A result at the alert level urges attention to the approaching action conditions. A result at the action level should prompt an investigation."	The phrase "more thorough investigation" implies that there are two levels of investigation, regular investigation and the more rigorous and in-depth "more thorough investigation." Nowhere in US GMP or FDA guidance is the difference explained. The first three sentences of this paragraph discuss the routine evaluation of data against action levels. This routine evaluation is not and should not be considered an investigation, but merely part of the routine monitoring and assessment of the environmental monitoring.

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				The words "more thorough" provides no more guidance as to what is required for investigations, or investigations in this particular case than does the single word "investigation." For this reason it is suggested that the words "more thorough" be deleted.
69.	1243-1244	"Written procedures should define the system whereby the most responsible managers are regularly informed and updated on trends and investigations."	"Written procedures should define the system whereby the responsible managers with the authority and responsibility to make improvements are regularly informed and updated on trends and investigations."	The phrase "most responsible managers" is not defined and is unclear. It may refer to variously the departmental management within the Quality Control Unit, the most senior management official at the site, or even the CEO of the firm. The lack of definition would lead to unnecessary citations for not providing routine trend analysis reports (which may show improvement) to CEOs. To clarify this sentence, it is suggested that the word "most" be deleted, and the responsible managers is further clarified by adding " with the authority and responsibility to make improvements."

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70.	1247-1249	"Environmental monitoring should include testing of various surfaces for microbiological quality. For example, product contact surfaces, floors, walls, ceilings, and equipment should be tested on a regular basis."	"Environmental monitoring should include testing of various surfaces for microbiological quality. For example, product contact surfaces, and equipment should be tested on a regular basis."	The environmental monitoring should concentrate on surfaces with realistic risk to product, so It should not be necessary to test ceilings and floors.
71.	1257-1259	"Therefore a sound disinfectant program also includes a sporicidal agent, used according to a written schedule and when environmental data suggest the presence of sporeforming organisms."	"Therefore a sound sanitization program also includes a sporicidal agent, used according to a written schedule and when environmental data suggest the presence of sporeforming organisms."	For consistency, since this section is about sanitization, it is suggested that the word "disinfectant" be changed to "sanitization." If not "sanitization", then "disinfection would be a better choice of words.
72.	1273-1275	"As part of methods validation, the quality control laboratory should evaluate what media exposure conditions optimize recovery of low levels of environmental isolates."	delete	Generally the procedure of methods validation in conjunction with microbial methods is not clear. The required method normally cannot be validated respectively it would be very complex and risky.

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73.	1297-1298	"Rapid genotypic methods are recommended for purposes of identification, as these methods have been shown to be more accurate and precise than biochemical and phenotypic techniques."	"Rapid genotypic methods may be used for purposes of identification. These methods have been shown to be more accurate and precise than biochemical and phenotypic techniques."	As other techniques are adequate for the purposes of identification, these binding recommendations should be generalized.
74.	1310-1312	"Monitoring of critical and immediately surrounding clean areas as well as personnel should include routine identification of microorganisms to the species (or, where appropriate, genus) level."	"Monitoring of critical areas as well as personnel operating within the critical areas should include routine identification of microorganisms to the species (or, where appropriate, genus) level. For clean areas, morphologically representative environmental monitoring isolates should be identified to species level, if possible."	The implication of "routine identification" implies that all colonies on all environmental monitoring samples should be identified, including those EM from clean areas. The suggested wording changes are in conformance with the PDA's "Points to Consider for Aseptic Processing" in PDA Journal of Pharmaceutical Science and Technology, Volume 57, number 2, 2003 Supplement, page 25. However, if the phrase "immediately surrounding clean areas" is meant to be the equivalent of the European GMPs "Class B" area, then it is suggested the wording be changed

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				to reflect this meaning. In this case, perhaps the sentence could read: "Monitoring of critical and immediately surrounding clean areas (e.g. those areas within the same room as the aseptic filling line, but outside the Class 100 curtained area) as well as personnel should include routine identification of microorganisms to the species (or, where appropriate, genus) level." As it stands, EM isolates from a Class 100,000 room next to the aseptic filling suite would be required to be 100% identified.
75.	1395-1396	"The batch processing circumstances – samples should be taken in conjunction with processing interventions or excursions."	delete	Processing interventions or excursions are covered by media f This sentence should be deleted, because during routine sterility sampling, potentially contaminated units are removed.
76.	1225-1226	"Nucleic acid-based methods are recommended for microbial identification purposes."	"Nucleic acid-based methods may be used for microbial identification purposes."	As other techniques are adequate for the purposes of identification, these binding recommendations should be generalized.

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77.	1226-1227	"Because of the limited sensitivity of the test, any positive result is considered a serious CGMP issue that should be thoroughly investigated."	"Because of the limited sensitivity of the test, any positive result is considered a serious CGMP issue that should be investigated."	The phrase "thoroughly investigated" implies that there are two levels of investigations, regular investigations and the more rigorous and in-depth "thorough investigations." Nowhere in US GMP or FDA guidance is the difference explained. The word "thoroughly" provides no more guidance as to what is required for investigations than does the single word "investigated." For this reason it is suggested that the word "thoroughly" be deleted.
78.	1441-1443	"A sterility positive result can be viewed as indicative of production or laboratory problems and should be investigated globally since such problems often can extend beyond a single batch."		The term "investigated globally" should be defined.
79.	1444-1446	"After considering all relevant factors concerning the manufacture of the product and testing of the samples, the comprehensive written	"After considering all relevant factors concerning the manufacture of the product and testing of the samples, the investigation should include specific	The phrase "comprehensive written investigation" implies that there are two levels of investigations, regular investigations and the more rigorous

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		investigation should include specific conclusions and identify corrective actions."	conclusions and identify corrective actions."	and in-depth "comprehensive investigations." Nowhere in US GMP or FDA guidance is the difference explained. The word "comprehensive" provides no more guidance as to what is required for investigations than does the single word "investigation." For this reason it is suggested that the word "comprehensive" be deleted. In addition, the GMP requirement is that investigations must be in written form. Specifying "written" in one case but not in the others implies that some investigations may not need to be written. Therefore it is suggested that the word "written" also be deleted.
80.	1484-1489	"Where a laboratory has a good track record with respect to errors, this history can help remove the lab as a source of contamination since chances are higher that the contamination arose from production. However, the converse	Where a laboratory has a good track record with respect to errors, this history can help remove the lab as a source of contamination since chances are higher that the contamination arose from production. However, the converse is not true. Specifically, where a laboratory has	The phrase "thoroughly investigated" implies that there are two levels of investigations, regular investigations and the more rigorous and in-depth "thorough investigations." Nowhere in US GMP or FDA guidance is the difference explained. The word

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		is not true. Specifically, where a laboratory has a poor track record, firms should not assume that the contamination is automatically more attributable to the laboratory and consequently overlook a genuine production problem. Accordingly, all sterility positives should be thoroughly investigated."	a poor track record, firms should not assume that the contamination is automatically more attributable to the laboratory and consequently overlook a genuine production problem. Accordingly, all sterility positives should be investigated.	"thoroughly" provides no more guidance as to what is required for investigations than does the single word "investigated." For this reason it is suggested that the word "thoroughly" be deleted.
81.	1609-1610	"In most sound designs, air showers over the critical zone once, and then is systematically exhausted."	"In most sound designs, air showers over the critical area once, and then is systematically exhausted."	The term "critical zone" is apparently used as a synonym to "critical area" as "clean zone" is cross-referenced to "clean area." As such, for consistency and clarity, it is suggested that all such references be changed from "critical zone" to "critical area."
82.	1683-1686	"A decontamination method should be developed that renders the inner surfaces of the isolator free of viable microorganisms. Decontamination can be accomplished using a number of vaporized agents, although these agents possess	"A decontamination method should be developed that renders the inner surfaces of the isolator free of viable microorganisms. Decontamination can be accomplished using a number of vaporized agents, although these agents possess limited capability to penetrate	The phrase "thorough determination" implies that there are two levels of determination, regular determination and the more rigorous and in-depth "thorough determination." Nowhere in US GMP or FDA guidance is the difference explained. The word

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		limited capability to penetrate obstructed or covered surfaces. Process development and validation studies should include a thorough determination of cycle capability."	obstructed or covered surfaces. Process development and validation studies should include determination of cycle capability."	"thorough" provides no more guidance as to what is required for a determination of cycle capability than does the single word "determination." For this reason it suggested that the word "thorough" be deleted.
83.	page 48, footnote	"If the various isolator materials are thoroughly evaluated during cycle development, a firm might consider placing more focus on material texture and porosity."	"Firms should include evaluation of isolator material and porosity which may make the decontamination more difficult during the quantified BI challenge of isolator decontamination efficacy.	The proposed wording clarifies the concern that the decontamination of different materials may be more difficult due to their porosity or other characteristics.
84.	1777-1778	"In addition, any other surface with the potential to contaminate the sterile product should be sterile."	"In addition, any other surface with the potential to contaminate the sterile product should be sterilized."	Elsewhere in the guidance, for instance, in line 552 where containers and closures are discussed, the term sterilized is used. For consistency and clarity, it is suggested that the term "sterilized" be used in place of "sterile" in this instance.
85.	1793-1794	"Furthermore, designs separating the filling zone from the surrounding environment are important to ensure product protection."	"Furthermore, designs separating the filling zone from the surrounding environment are important to ensure product protection."	The word "zones" is not defined and is used alternately with "area". For consistency, it is suggested that the word "zone" be replaced by "area" throughout.

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86.	1847	"sterilyze"	"sterilize"	Correct the spelling.
87.	1857	"sterilyzed"	"sterilized	Correct the spelling.
88.	1989-1990	"Barrier- A physical partition that affords aseptic manufacturing zone protection by partially separating it from the surrounding area."	"Barrier- A physical partition that affords aseptic manufacturing area protection by partially separating it from the surrounding area."	The word "zones" is not defined and is used alternately with "area". For consistency, it is suggested that the word "zone" be replaced by "area" throughout.
89.	page 59, glossary reference: lines 202, 698, 757, 794, 837, 906, 914, 979, 994, 1008, 1015, 1586,		Justification - Establishing documented evidence, usually based upon historical operational data or accepted scientific theory, that supports the process or establishes limits or action levels.	The words "justified" and "justification" occurred several times in this guidance, as does "validation" and "qualification." Because both words occur, there is a difference between justification and validation. While there is a FDA guidance document defining what validation is

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	1691, 1693, 1706 and 1781			and consists of, there is no document defining what "justification" is or entails. Adding this definition provides minimal guidance to show that there is a difference in level of documentation and requirements for "justification" as opposed to "validation."
90.	2013	Clean Zone- See Clean Area.	delete.	The term "clean zone" is not used in the document, and therefore is not needed in the glossary. It is suggested that this glossary entry be deleted.
91.	2015-2017	"Critical surfaces- Surfaces that may come into contact with or directly affect a sterilized product or its containers or closures. Critical surfaces are rendered sterile prior to the start of the manufacturing operation, and sterility is maintained	"Critical surfaces- Surfaces that come into contact with a sterilized product or the product contact surfaces of its containers or closures. The interior of the elastomeric closure hopper on the aseptic filling line is a critical surface as it touches the sterilized product contact surface of	The first sentence of the definition is too broad or could be broadly interpreted by an inspector to include all equipment in the filling area. The suggested change is to specify the critical surfaces as only those in contact with the sterilized product or

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		throughout processing."	the elastomeric closure. The conveyor belt under a vial on the aseptic filling line is not a critical surface as it does not touch the sterilized product contact surface of the vial, which is the inside."	sterilized containers and closures. The second sentence is a requirement, and as such should not be contained in a glossary. Such requirements, if necessary, belong the guidance proper, and it is suggested that the second sentence therefore be deleted from the glossary definition. The examples provided in the suggested wording give a more clear understanding of where the definition applies and do not apply.
92.	2047-2049	"Intervention- An aseptic manipulation or activity that occurs at the critical zone." and "Closed isolator systems exclude external contamination from the isolator's critical zone by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment."	"Intervention- An aseptic manipulation or activity that occurs in the critical area." "Closed isolator systems exclude external contamination from the isolator's critical area by accomplishing material transfer via aseptic connection to auxiliary equipment, rather than use of openings to the surrounding environment."	The term "critical zone" is apparently used as a synonym to "critical area" as "clean zone" is cross-referenced to "clean area." As such, for consistency and clarity, it is suggested that "at the critical zone" be changed to "in the critical area."

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93.	lines 704, 708, 765, 768, 1066, 4069, 1087, 1096, 1222, 1624, 1797, 1806, 1814	"qualification"	"validation"	There is no definition in this guidance as to what qualification is or means as opposed to validation which is defined within the glossary. For consistency and clarity, it is suggested that the single term "validation" be used and will be understood to mean the appropriate studies necessary. If there is a specific meaning implied by "qualification," then it is suggested that the glossary be updated or enough details be provided in the text to fully explain the meaning at that point.
94.	lines 645, 808, 945	"vials"	"containers" or perhaps to "containers, such as vials,"	Throughout the rest of the guidance the term "containers" is used. With perhaps the exception of line 645, container is the more general term and it is suggested it be used for consistency within the guidance.