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Re: USP Revision to Chapter <1229.19> Simultaneous Decontamination and Sterilization and Chapter <1229.20> Decontamination and Sterilization Pre, Mid and Post Process Considerations

Dear Dr. Tirumalai,

PDA appreciates the opportunity to comment on USP's recent development of Chapters <1229.19> and <1229.20> where USP is providing guidance on decontamination and sterilization. PDA supports USP's efforts to enhance guidance in this important area of manufacture for sterile products. The PDA commenting committee, made up of members with experience and expertise in the chapter subject matter, has developed detailed comments which are provided below. Several of the comments addressed the need for further clarity. Our concern, in part, is that where members of this commenting committee were unsure of the intent of a statement or position, it is likely that other users would have similar difficulty.

PDA strongly recommends that USP review the language surrounding some of the recommendations made and provide clarity as indicated within the comment table attached to this letter for both chapters. There is a risk of USP introducing contradictory guidance and setting unintended requirements with the recommendations made. Such unintended consequences would not be beneficial for global patients, regulators, or manufacturers.

PDA offers specific feedback for your consideration:

A clear definition of "simultaneous decontamination and sterilization" would be helpful to aid users in better understanding the scope and application of <1229.19>.

Sterilization with vapor phase agents included in <1229.19>, may be recognized as less robust than traditional sterilization modalities by certain regulatory authorities and industry organizations. There is a lack of alignment between the approaches in this chapter and the recognized sterilization methods (e.g., overkill, etc.) detailed in <1229> that are required to support the achievement and demonstration of probability-based sterilization.

The "estimated" spore log reduction (SLR) values used in <1229.19> to support the efficacy of the microbiological inactivation process are significantly greater than the log

order of the biological indicator starting population without explanation or citation of a supporting peer-reviewed reference.

New and impractical requirements, such as the addition of bioburden population and resistance testing of interior surfaces of aseptic processing environments prior to exposure to microbiological inactivation processes are included.

Although, the term “decontamination” is included in the title for <1229.20>, the use of this process type is not included in the body of the chapter. An updated title that more precisely defines the scope and content of this chapter is needed.

The use of terminology related to microbiological inactivation and other topics is inconsistent and, in some cases, technically inaccurate. For example, the term disinfection is used in <1229.20> in several instances in place of the term “sterilization”.

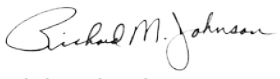
Several of the claims stated in the chapter, including those noted in this letter, do not appear to be supported by the end of chapter references. We recommend that those supporting references be added and other indicated irrelevant references be removed.

Based on the lack of terminology/language clarity and scientific clarity related to the content and application of these chapters as indicated in the comments and feedback provided, PDA strongly recommends addressing the concerns noted in our comments prior to publishing the chapters. PDA would be happy to collaborate with USP in the continued development of this guidance. Like USP, PDA is also committed to advancing science to support product quality and patient safety, and the topics covered by this guidance are of special interest throughout our organization.

PDA is a non-profit international professional association of more than 10,000 individual member scientists having an interest in the fields of pharmaceutical, biological, and device manufacturing and quality. Our comments have been prepared by a committee of global experts in decontamination, sterilization, and sterility assurance on behalf of PDA’s Science Advisory Board and Board of Directors.

If you have any questions, please do not hesitate to contact me.

Sincerely,



Richard Johnson
President and CEO

cc: Janie Miller, PDA

PDA Comments to USP Revision to Chapter <1229.19> Simultaneous Decontamination and Sterilization (2021)

Section	Reference Text (Please specify exact text)	Editorial or Technical (E/T)	Comment to Specific Text	Rationale / Alt Text (Must be provided if mandatory/technical comment)
General Comment	Simultaneous Decontamination and Sterilization	T	This chapter does not broadly apply to all decontamination/sterilization modalities, but this is not clearly conveyed by the title.	Update Title: Simultaneous Decontamination and Sterilization of Aseptic Processing Equipment and Enclosed Environments with Gaseous and Vapor Phase Sterilants
Intro	See Intro	T	A formal definition for simultaneous decontamination and sterilization would be helpful.	Simultaneous decontamination and sterilization is defined as the single application of a gaseous or vapor phase sterilant to the external surfaces of aseptic processing equipment and internal surfaces within an enclosed environment (i.e., closed chambers, isolators, separative enclosures, passthroughs, cleanrooms and process equipment contained in these spaces) to simultaneously accomplish sterilization for surfaces that are required to be sterile and decontamination of all other surfaces including those that may be sensitive to the sterilant.
Intro	…is useful where the complete absence of microorganisms on some surfaces, but not all, is desired.	T	This statement allows for the presence of micoorgnanisms on some surfaces within the aseptic processing environment. Focus of statement should be modified to focus on the achievement of sterilization and disinfection.	...is useful where sterilization of some surfaces, but not all, if allowed and where other controls are in place to ensure that organisms cannot be transferred to from decontaminated to sterilized surfaces.
Intro	Because the decontamination and sterilization processes described typically render the entire work environment free of viable microorganisms, the adjacent surfaces become simultaneously sterilized surfaces, and internal items need no further protection, provided system integrity is maintained.	T	"Free from viable organsims" is the definition of sterile which does not apply to decontamination. What is meant by adjacent surfaces? Depending upon the lethality challenge for adjacent surfaces and whether sterilization or decontamination has been validated, the adjacent surfaces cannot be assumed to be sterilized.	Because the properly validated decontamination and sterilization processes yield an enclosed work environment that contains a low level of or is completely free of viable microorganisms, these surfaces need no further protection, provided system integrity is maintained.
Intro	These processes are often used for in situ treatment of large controlled environmental systems.	T	What is meant by large controlled environmental systems?	Provide clarification and example(s) (is this Grade A Rooms, large facilities, etc.?) of large environmental systems.

Intro	Sterilization of these controlled environmental systems in their entirely is not desirable, due to the potential damage to materials and components not required to be sterile because of extended process conditions.	T	The desire is always to be sterile wherever possible-so would not state this is not desirable. Rather the point should be that a control strategy which considers an appropriate balance of sterilization and decontamination can afford a robust control strategy that yields an environment that is demonstrably free of viable organisms without damage to materials and components.	A control strategy which considers an appropriate balance of sterilization and decontamination can afford a robust control strategy that yields an environment that is demonstrably free of viable organisms without damage to materials or components. The control strategy should be based on formal quality risk management principles with due consideration of product contact surfaces for which sterilization is a requirement. It would also be helpful to provide clarification and example(s) (is this Grade A Rooms, large facilities?) of what specific items/materials are likely to be affected.
Intro	Surfaces expected to be decontaminated would use a lower population (10^3 to 10^4) spores per unit) of a resistant biological indicator (BI) consistent with regulatory expectations.	T	What reference or rationale supports the use of this BI log order for decontamination? <1208> from 2011 or earlier states a 2-3 log reduction for Sterility Testing Isolator, but this is obsolete now 10 years later. FDA's 2004 Aseptic Processing Guidance requires a 4 to 6 BI spore log reduction with indication that a 4 spore log reduction should be sufficient for controlled, very low bioburden materials introduced into a transfer isolator. A common industry requirement is a 6 log reduction which typically is not difficult to achieve. ~~Al~~ Additionally, this statement is incomplete since, while it provides BI starting populations, it does not provide minimum requirements for spore log reduction acceptability for decontamination.	Recommend the inclusion of supporting details, scientific/mathematical-based rationale and regulatory or peer-reviewed reference(s) that support the acceptability of a 10^3 to 10^4 BI for validation of decontamination.

Introduction	Log kill, as described in several of the reference documents, is interpreted as no recovery of the stated challenge population, thus affording a minimum 2-3 log greater reduction when no positive BI's are found post-process (assumes replicate studies with multiple BIs in each study).	T	The specific mathematic and scientific basis must be provided to support this statement and the values presented in Figure 1. If the use of the MPN approach is the basis for "taking credit" for an 3 log reduction increase above the log order of the BI starting population, this must be clearly presented (ideally with examples) with the understanding that this approach is only valid if each set of replicates analyzed was exposed to a homogenous treatment by the lethal agent (this is typically not the case unless replicates are directly adjacent to each other within the aseptic environment). Additionally, why is complete inactivation required? Log kill can still be demonstrated with BI survivorship. For example, fractional BI inactivation results with at least one positive test article (when two or more replicates are placed at a discrete location) can still be used to calculate a valid spore log reduction value.	Provide a description, details, scientific/mathematical-based rationale and supporting peer-reviewed references for the statement "thus affording a minimum 2-3 log greater reduction when no positive BI's are found" presented in Figure 1. A technical rationale to must be cited or provided to support the requirement for the use of a 6 log BI along with including a description of how complete inactivation of a 6 log BI supports an estimated 8-9 log reduction. Additionally, since this document may be used as a standard by regulatory authorities, scientifically sound and precise values (not estimates) should be provided for all critical values (e.g. estimated log reduction values) referenced.
Under Figure 1	Surfaces to be sterilized should use a higher challenge population (10^6) per unit of a resistant BI with the expectation of no recoverable microorganisms post-process.	T	There is no currently recognized definition or approach for the demonstration sterility using VHP in an isolator in currently recognized guidances or standards including the 2004 FDA Aseptic Processing Guidance or PDA's Points to Consider for the Aseptic Processing of Sterile Pharmaceutical Products in Isolators (2020). How does complete inactivation of the 10^6 BI meet the requirements to demonstrate the achievement of sterilization/sterility? USP <1229> indicates that sterility "is defined in probabilistic terms". How is probability (i.e., PNSU) and either of the 3 cycle design methods (e.g., Overkill, etc.) specified in in <1229> used to demonstrate sterility?	Provide a description, details, scientific/mathematical-based rationale and supporting peer-reviewed references to support that complete inactivation of a 10^6 BI is valid for demonstrating sterility.
Under Figure 1	This provides an estimated 8-9 log reduction.	T	See comment on "log kill" above for Introduction.	See comment on "log kill" above for Introduction.

Under Figure 1	…on previously cleaned surfaces…	T	Cleaning must be validated and performed before decontamination or sterilization.	Cleaning must be validated to ensure that oily residues or other substances that can reduce the effectiveness of the decontamination process are removed prior to its application.
Under Figure 1	Consistent with these processes, the pretreatment bioburden is evaluated to confirm that it is less resistant to the chosen agent and less populous than the BI microorganism chosen, affording greater confidence in the outcome.	T	This statement constitutes a new, unnecessary and impractical requirement for the testing for bioburden population and resistance on surfaces to be treated with a lethal agent. <1229.11> on vapor phase sterilization, which highlights the complexities and issues with determination of microorganism resistance with VHP (most commonly used agent for this application), does not contain a similar requirement for population/resistance determination with VHP processes. Sampling for bioburden in these environments may also represent a potential contamination issue.	Delete this statement.
Under Figure 1	…must be fully exposed…	T	The cleaning aspect is most important for the Decontamination Cycle , refer to PTC Isolators.	…must be clean and fully exposed…
Under Figure 1	Effectiveness of the disinfection process…	T	Need consistency with the use of terms-sterilization is not considered a subprocess under the general heading of disinfection. Is disinfection being utilized to include both decontamination and sterilization--this is inappropriate.	Effectiveness of the microbiological inactivation process…
Under Figure 1	This will prevent the ingress of microbial contamination after the disinfection process…	T	Need consistency with the use of terms-sterilization is not considered a subprocess under the general heading of disinfection. Is disinfection being utilized to include both decontamination and sterilization--this is inappropriate.	This will prevent the ingress of microbial contamination after the microbiological inactivation process…
Validation	The cycle development and validation approaches for these disinfection processes, described in <1229> and <1229.11>,	T	Need consistency with the use of terms-sterilization is not considered a subprocess under the general heading of disinfection. Is disinfection being utilized to include both decontamination and sterilization--this is inappropriate.	The cycle development and validation approaches for these microbiological inactivation processes, described in <1229> and <1229.11>,

Empty Chamber Parameter Distribution	BIs are not required in the evaluation of the empty chamber).	T	In consideration of an Isolator (or even RABS) - wouldn't the "empty chamber" configuration be typical for operations (i.e. before use)? Why is no BI needed in this scenario? The use of an example would be helpful to describe meaning of an empty chamber and the purpose of the associated study.	Depending upon the enclosed area and the purpose of the study, BIs may not always be required (e.g., engineering study in the evaluation of the empty chamber).
Load Item Mapping	For surface treatment, internal mapping of load items is not required.	T	Strengthen statement to indicate why load mapping is not required.	Since all surfaces that are intended to be decontaminated or sterilized must be fully exposed and directly accessible to the decontamination or sterilization agent, internal mapping of load items is not required.
Biological Indicators	The preference is to use BIs from the same lot with different populations…	T	Since the performance of a BI lot is certified with a singular population, it is not possible to use BI's from the same lot with different populations.	Delete statement or indicate that it is recommended to use BI lots with different/graded population levels with similar Dvalues wherever possible.
References	1. Parenteral Drug Association. PDA Technical Report No. 28…		Remove PDA Technical Report No. 28 as its content is not relevant to this point. Add reference to PDA Points to Consider for the Aseptic Processing of Sterile Pharmaceutical Products in Isolators (2020).	Replace with: Parenteral Drug Association, Points to Consider for the Aseptic Processing of Sterile Pharmaceutical Products in Isolators (2020)

PDA Comments to USP Revision to Chapter <1229.20> Decontamination and Sterilization Pre, Mid and Post Process Considerations (2021)

Section	Reference Text (Please specify exact text)	Editorial or Technical (E/T)	Comment to Specific Text	Rationale / Alt Text (Must be provided if mandatory/technical comment)
General	Entire Document	E	Many sections of this document have excessively prescriptive requirements.	Why wouldn't the applicable sterilization/decontam chapters cover these specifics as they relate to the modality? Is this intended to inclusive of only moist heat sterilizer chambers used for sterilization? If only sterilizer chambers, references to decontam (title) should be removed as there are several sections/statements which refer exclusively to sterilization and consideration of decontamination is not present at all in this document.
Title	Decontamination and Sterilization Pre, Mid and Post Process Considerations	T	This chapter has a similar title to 1229.19, but covers additional and different processes and products including wrapped items but not enclosed environments such as isolators and does not broadly apply to all decontamination/sterilization modalities, but this is not clearly conveyed by the title. The content of this chapter seems to exclusively apply to items sterilized in chambers. It does not appear that decontamination is considered in any of the topics covered by this chapter. The use of the terms "pre, mid and post" in the title is and unnecessary.	Sterilization of Items and Products: Process Considerations
Introduction	The decontamination and sterilization of equipment,…	T	The content of this chapter seem to exclusively apply to items sterilized in chambers. It does not appear that decontamination is considered in any of the topics covered by this chapter.	The Introduction should be updated to clearly convey the scope and applicability of this chapter.
Preprocessing Activities	These may be conducted at any time prior to the start of the sterilization cycle.	T	This statement is specific to sterilization--are decontamination processes not subject to this document? Sterilization is used exclusively and repeatedly in this document even though the title indicates that decontamination is subject to this document.	See comment on Title/Introduction above.
Wrapping and Container Controls	Flexible wrapping materials hold be subject to quality standards including material controls, porosity, and shelf life…"	T	The performance of barrier properties should be included in this statement as porosity is the incorrect term.	Flexible wrapping materials should be subject to quality standards including material controls, final configuration controls and microbial barrier performance over shelf life.
Cleaning of Materials	N/A	T	Cleaning should be validated for reprocessed items and other items that are cleaned prior to sterilization.	Add statement: Cleaning procedures must be validated for reprocessed items and other items that are cleaned prior to decontamination or sterilization.

Wrapping and Container Controls	N/A	T	Packaging materials and configurations should be qualified as sterile barriers.	Add Statement: For sterilized products, the material and configuration used as the primary packaging sterile barrier should be qualified.
Load Wrapping and Preparation	Section Title: Load Wrapping and Preparation	E	Load is not wrapped, items are wrapped.	Item Wrapping and Preparation
Load Wrapping and Preparation	The orientation of items, including tubing length, positions of valves...	E	Tubing length is not an orientation attribute.	The orientation of items, including tubing, positions of valves...
Load Wrapping and Preparation	Where appropriate, sterilization indicators should be placed on wrapped or contained items, or externally to confirm process lethality.	T	Sterilization indicators (e.g., chemical indicators) may only provide evidence of an exposure to a general sterilizing condition (e.g., steam/heat), but cannot not necessarily confirm the achievement of a lethality. For example, with moist heat sterilization, the only two methods to confirm process lethality are with F0 calculations and/or BI's. However, F0 calculations and BIs are only employed during validation cycles and chemical indicators cannot be used to demonstrate achievement of sterilization. Wherever possible, please add specific guidance on sterilization indicators including reference to 1229.9 at the end of this chapter.	Where appropriate, sterilization indicators should be placed on wrapped or contained items, or externally to confirm exposure to the process.
Load Placement	The individual load items must be placed and oriented into position as required by the operating instruction.	T	"Load Placement": a key- aspect is missing, that the "operating instruction" must be better explained, e.g. that the loading configuration must be identical to the load which has been used/ validated in the Qualification runs.	The individual load items must be placed and oriented into the positions as required by the validation and operating instruction.
Material and Load Inspection	…, they should be inspected for evidence of damage, torn wrapping and /or covers, color changes, excess condensation, ...	T	Any condensation present after processing could allow for the wicking of microorganisms through the permeable packaging.	…, they should be inspected for evidence of damage, torn wrapping and /or covers, color changes, condensation on or inside of packaging, ...
Material and Load Inspection	Any anomalous indicator result should be immediately reported to supervisory personnel.	T	Any failed indicator should be investigated for cause and product impact.	Any anomalous indicator result should be immediately addressed according to written procedures.

Deviation Reporting	The operator should report and record any unusual occurrences during the execution of the sterilization process, including sounds, odors, leaks or other atypical events, and should respond as instructed to any audible or visual alarms related to the process.	T	Sounds and odors during the sterilization process are not always objective, readily measurable or definable.	The operator should report and record any unusual occurrences during the execution of the sterilization process, including leaks or other atypical events, and should respond as instructed to any audible or visual alarms related to the process.
Post-Process Documentation Review	The operator should recover the sterilizer printout, recorder charts and other relevant process information for inclusion in the sterilization cycle records.	T	Need to refer broadly to sterilization records as these are often electronic records.	The operator should review the sterilizer records and other relevant process information including chemical indicator results to ensure that all key and critical parameters were met. If any key or critical process parameter is not met, a formal investigation should be conducted to identify cause and determine impact to product.
Personnel Training	Operators and supervisors must be trained in the fundamentals of sterilization microbiology, and must adhere to instructions for sterilization.	T	Training sterilization microbiology is not necessarily required for sterilizer operators.	Operators and supervisors should be trained in the fundamentals of sterilization microbiology, and must adhere to instructions for sterilization.
Conclusion	The proper utilization of sterilization equipment is central to the elimination of micoorgnanisms in a variety of settings.	T	The lethal processes that are the subject of this chapter inactivate microorganism but do not eliminate (filtration) microorganism.	The proper utilization of sterilization equipment is central to the inactivation of microorganisms in a variety of settings.