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22 March 2024

Leslie Furr, Associate Scientific Liaison
USP Compendial Science
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Rockville, MD 20852

Reference: USP Chapter <1119> Bioburden Monitoring

Dear Madam or Sir,

PDA appreciates the opportunity to provide feedback to the USP Microbiology Expert Committee on the proposed addition of the new chapter for Bioburden Monitoring <1119>. In our attached comments, PDA offers specific comments and feedback that we believe will be helpful in the further development of this important Chapter.

PDA is a non-profit international professional association of more than 10,000 individual members comprising scientists, industry professionals and consultants having an interest in fields of pharmaceutical, biological, device manufacturing, and quality. Our comments have been prepared by a committee of PDA members with expertise in the areas covered in the Public Docket on behalf of PDA's Science Advisory Board.

If you have any questions, please do not hesitate to contact me via email at wright@pda.org.

Sincerely,

Glenn E. Wright
President and CEO

cc. Josh Eaton,PDA; Carrie Horton,PDA; Jessie Lindner, PDA; Danielle Bretz, PDA

USP <1119> Bioburden Monitoring

General Comments		
Comment to Text	**Proposed Change**	**Rationale for Change**
Throughout the document, the terms “limit”, “specification” and “acceptance criteria” are used. PDA recommends avoiding the use of these terms due to variations in reader interpretation and these terms are typically interpreted with release testing which is not covered within the scope of this Chapter.	PDA suggests the use of the term “level(s)” in place of the currently used terms of “limit(s)” “acceptance criteria” or “specification”.	The scope of this chapter is for bioburden monitoring and not release testing; therefore, the term “level” more accurately reflects the scope of this Chapter.
Throughout the document, the term “sample location” is used. PDA recommends the use of an alternative term to “location”. The term “location” gives the limited connotation of a specific physical location whereas the scope of this chapter also addresses points of a water system as well as points during the manufacturing process.	PDA suggests using the term “sample point” in place of “sample location”.	Changing the terminology from “sample locations” to “sample points” clarifies the intent and will more accurately represent the bioburden sample types found within the scope of this Chapter.
There is no guidance around the response to take if the bioburden test exceeds the bioburden level. PDA recommends including some guidance to address this topic.	PDA recommends adding guidance regarding the response to take if bioburden level is exceeded.	Addition of this element will complete the lifecycle of the bioburden sample through the handling of the bioburden data as currently the chapter ends at completion of the test and guidance around recommended bioburden levels.

Section: Introduction			
Current Text	**Comment to Text**	**Proposed Change**	**Rationale for Change**
"When faced with a decision regarding the quantification of microorganisms (bioburden) or performing a microbial enumeration test purposed for the examination of nonsterile products, refer to the decision tree, Figure 1, in the Appendix. The scope of this chapter includes any material subject to a test for bioburden that is not used for the release testing of finished product, and which a test is not described in a monograph; this includes but is not limited to, in-process samples, drug substances, components, and water."	PDA suggests providing further clarification regarding the scope of this chapter. Specifically, the scope of this chapter could be read to apply to materials used for classical non-sterile products. However, it appears from the context of the chapter (especially the content found in Table 2: Considerations for Bioburden Test User Requirements) that it applies to materials that will be used to manufacture sterile products (e.g. biologics). Additionally, PDA suggests relocating the first sentence to after the sentences clarifying scope to improve flow.	"The scope of this chapter includes any material **intended for use in the manufacture of low bioburden and sterile products** that is subject to a test for bioburden **as defined per <1117.1>**; this includes but is not limited to, in-process samples **(e.g., sample stages upstream and before final bioburden reduction in case of bioproducts and sterile filtration in case of sterile drug products),** drug substances, components, and water. **The scope of this chapter does not include release testing of finished product, scope per <1111>, or a test described in a monograph.** When faced with a decision regarding the quantification of microorganisms (bioburden) or performing a microbial enumeration test proposed for the examination of nonsterile products, refer to the decision tree, Figure 1, in the Appendix."	This additional language will ensure clarity for the reader in understanding the intended scope of this chapter. Relocating of the first sentence provides improved flow with the scope being defined and then referring to the appendix for additional guidance when deciding if within scope of chapter.
"In other cases, however, a different type of bioburden may be anticipated, and this would require modification of the method described in ⟨1119.1⟩."	PDA recommends expanding the scope to include not only modification of the method described in ⟨1119.1⟩, but also including reference to 1223 for an alternative suitable, validated method: *Validation of Alternative Microbiological Methods.*	"In other cases, however, a different type of bioburden may be anticipated, and this would require **either the** modification of the method described in ⟨1119.1⟩, **or the use of an alternative suitable, validated method ⟨1223⟩.**"	By including methods from Chapter ⟨1223⟩, this enables the selection of the appropriate method based on the nature of the bioburden present and ensuring appropriate method suitability assessment.

Section: Introduction			
Current Text	**Comment to Text**	**Proposed Change**	**Rationale for Change**
"Bioburden monitoring is a critical activity in the manufacture of nonsterile, low-bioburden, and sterile pharmaceuticals executed upon a diverse range of sample types."	PDA suggests using alternative language for 'executed upon' because this wording could be misinterpreted.	"Bioburden monitoring is **an important piece of the contamination control strategy** in the manufacture of nonsterile, low-bioburden, and sterile pharmaceuticals **performed for** a diverse range of sample types."	This proposed wording makes it clear to the reader that testing is being discussed.
"The purpose of bioburden monitoring is to ensure that the microbial load remains acceptable to ensure the item consistently meets the required acceptable limit for bioburden."	PDA recommends elaborating the current wording to provide an explicit reason for why there would be a need to perform analysis of the bioburden of the item.	"The purpose of bioburden monitoring is to ensure that the microbial load remains acceptable to ensure the item consistently meets the required acceptable **level** for bioburden **in support of the overall contamination control strategy**."	By adding this clarifying statement, the reader is explicitly informed of the reason an analysis of bioburden would be needed and they are directed to link this action to their microbiological contamination controls. Additionally, this proposed wording is aligned to the wording found in the European Commission Guidance Document "Annex 1: Manufacture of Sterile Medicinal Products, EudraLex-Volume 4-EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use, 2022".
"Where necessary, bioburden monitoring can also be used to ensure the effectiveness of any subsequent sterile filtration or terminal sterilization process."	PDA feels the intent of this statement may not be clear to the reader and may be misinterpreted as bioburden monitoring following sterilization processes.	"Where necessary, bioburden monitoring can also be used to **assess that the microbial load is acceptable prior to** sterile filtration or terminal sterilization **to ensure effectiveness of the sterilization processes**."	Providing this clarifying wording offers additional clarity to the reader that the intention was around assessing microbial load prior to sterilization. Therefore, the bioburden monitoring would be prior to the sterilization process.

Section: Introduction			
Current Text	**Comment to Text**	**Proposed Change**	**Rationale for Change**
"Creating an effective bioburden monitoring program begins with an assessment of the manufacturing and/or operational processes, followed by the development and implementation of a risk-based sampling and testing regimen. A bioburden program must include appropriate sample locations, sample volumes, and test methods."	PDA recommends adding text which discusses the use of existing manufacturing process reviews and risk assessments information as part of the creation of a bioburden monitoring program. Additionally, PDA recommends including language around the use of process analytical technology.	"Creating an effective bioburden monitoring program begins with an assessment of the manufacturing and/or operational processes, followed by the development and implementation of a risk-based sampling and testing regimen. A bioburden program must include appropriate sample **points**, sample volumes, and test methods. **Where available, leverage relevant information from existing process reviews and risk assessment. If process analytical technology is implemented, describe any bioburden analysis strategy, such as on-line or in-line testing."**	Manufacturers of drugs and biologics are likely to have detailed manufacturing process reviews and risk assessment(s). Portions of this information would be focused on microbial contamination which can be utilized in establishing a sampling and testing regime. Accounting for newer technologies/platforms involving on-line or in-line testing versus grab samples.
"The companion test method (see ⟨1119.1⟩) must be developed and proven suitable for the sample tested. Other methods are permissible, but these must be developed and validated per *Validation of Alternative Microbiological Methods* ⟨1223⟩."	PDA agrees that readers should be directed towards USP Chapter ⟨1223⟩ for guidance. However, PDA encourages the provision of clarification for the reader regarding the requirement to follow this Chapter as guidance solely.	"The companion test method (see ⟨1119.1⟩) must be developed and proven suitable for the sample tested. Other methods are permissible, but these must be developed and validated. **For guidance on validation, refer to** *Validation of Alternative Microbiological Methods ⟨1223⟩***"**	By providing direction for the reader to refer to Chapter ⟨1223⟩ for guidance, it clarifies that other suitable approaches to validation of the method can be used as well.

Section: Risk-Based Bioburden Monitoring			
Current Text	**Comment to Text**	**Proposed Change**	**Rationale for Change**
"A formal documented assessment of risk using appropriate management tools (e.g., International Council for Harmonisation ICH Q9) should be used to identify appropriate points for monitoring of bioburden."	PDA encourages updating this sentence to clarify that the intent is about risk assessment not 'management tools'.	"A formal documented **risk assessment** using **appropriate tools** (e.g., International Council for Harmonisation ICH Q9) should be used to identify appropriate points for **bioburden monitoring**."	By rewording the sentence, this will improve clarity for the reader.

"The bioburden monitoring risk assessment should include, but not be limited to, the following: • Microbiological attributes of materials used in the process (e.g., raw materials, excipients) • Origin of materials (e.g., natural, semisynthetic, synthetic) • Inherent antimicrobial properties of the materials • Water activity of the material • Environmental conditions within the facility (e.g., classification status of cleanrooms) • Equipment design and cleaning • Open and closed processes • Process steps and activity duration • Storage conditions • Sanitization, decontamination, and other active microbial control processes (e.g., filtration, temperature, pH, osmolarity, water activity) • Number of samples and quantities (volumes, weights, or units) to test • Frequency of testing"	PDA recommends removing the example of "classification status of cleanrooms" associated with the bullet for facility environmental conditions. PDA suggests adding bullet points for additional items to be included in the risk assessment where available: • Organism expected and/or represent increased risk to manufacturing process • Review of historical data	"The bioburden monitoring risk assessment should include, but not be limited to, the following: • Microbiological attributes of materials used in the process (e.g., raw materials, excipients) • Origin of materials (e.g., natural, semisynthetic, synthetic) • Inherent antimicrobial properties of the materials • Water activity of the material • **Environmental conditions within the facility** • Equipment design and cleaning • Open and closed processes • Process steps and activity duration • Storage conditions • Sanitization, decontamination, and other active microbial control processes (e.g., filtration, temperature, pH, osmolarity, water activity) • Number of samples and quantities (volumes, weights, or units) to test • Frequency of testing • **Type of organisms expected and/or those that represent increased risk to the manufacturing process.** • **Historical trending of bioburden testing, if available**"	Some facilities that will be following this Chapter guidance will not have classified cleanroom areas. By removing the example of "classification status of cleanrooms" this will eliminate possible confusion but remain true to the bullet's intent of "environmental conditions within the facility". Accounting for the type of organism is a critical element to the risk assessment to understand normal flora versus shift in type of organisms and certain types of organisms can have an increased impact to manufacturing processes, e.g., in particular for sterilization steps. The review of trending provides the opportunity to assess any potentially problematic sampling areas. This trending data may not be available in all circumstances so the caveat "if available" was included.

Section: Risk-Based Bioburden Monitoring			
Current Text	**Comment to Text**	**Proposed Change**	**Rationale for Change**
"The bioburden risk assessment should be performed by a cross-functional team that is knowledgeable in the manufacturing process and microbiology. The risk assessment should be reviewed periodically and when any substantive changes occur to the manufacturing process."	PDA recommends that "manufacturing process" be reworded to expand the scope for when a risk assessment should be reviewed.	"The bioburden risk assessment should be performed by a cross-functional team that is knowledgeable in the manufacturing process and microbiology. The risk assessment should be reviewed periodically and when **changes are made to any risk-assessment parameters**."	This change will clarify for the reader to link back to the elements assessed as part of the risk assessment when determining changes that would trigger a risk-assessment review. This will direct the reader to take a more wholistic approach.

Section: Bioburden Sampling			
Current Text	**Comment to Text**	**Proposed Change**	**Rationale for Change**
Table 1. Considerations for Bioburden Sampling <u>Topic: Guidance and recommendations</u> "Identify relevant regulatory guidance for the control and monitoring of bioburden, sampling volumes, and frequency. Examples of relevant regulatory guidance: • Microbiological Quality Considerations in Non-Sterile Drug Manufacturing. Guidance for Industry (1). • Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice. Guidance for Industry (2). • Sterile Drug Products Produced by Aseptic Processing. EMA/CHMP/CVMP/850374/2015. Guideline on the Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container (3)."	PDA proposes to update the list of relevant regulatory guidance. The following updates are suggested: 1. Remove "Microbiological Quality Considerations in Non-Sterile Drug Manufacturing. Guidance for Industry (1)". 2. Add the below and renumber references accordingly: • ISO 13408-Aseptic Processing of Health Care Products: 2023 • ANSI/AAMI/ISO 11737-1 Sterilization of Health Care Products- Microbiological Methods: 2018 • EU GMP Annex 1: Manufacture of Sterile Medicinal Products: 202 Additionally, it seems there is an editorial error in the third bullet point. "Sterile Drug Products Produced by Aseptic Processing" appears to be erroneously duplicated in this regulatory guidance listing.	*Table 1. Considerations for Bioburden Sampling* <u>Topic: Guidance and recommendations</u> "Identify relevant regulatory guidance for the control and monitoring of bioburden, sampling volumes, and frequency. Examples of relevant regulatory guidance: • **ANSI/AAMI/ISO 11737-1 Sterilization of Health Care Products- Microbiological Methods: 2018 (1).** • **EU GMP Annex 1: Manufacture of Sterile Medicinal Products: 2022 (2).** • **ISO 13408-Aseptic Processing of Health Care Products: 2023 (3).** • Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice. Guidance for Industry (4). • ~~Sterile Drug Products Produced by Aseptic Processing.~~ EMA/CHMP/CVMP/850374/2015. Guideline on the Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container (5)."	Proposed changes will help to avoid the reader incorrectly applying this chapter to materials covered under USP <1111> and <61> (non-sterile drugs) that are outside of the scope of this new chapter. The additional references are applicable to the scope of this chapter and provide additional guidance to the reader.

Table 1. Considerations for Bioburden Sampling <u>Topic: Sample location</u> "Define where in the manufacturing and/or operational processes samples are taken as determined through a risk assessment. Examples of sampling locations include but are not limited to: • Following cleaning and clean hold times for product-contact equipment • Prior to filling a primary container for a nonsterile product • During different stages of biologics manufacturing, such as bioreactor media, end-of-production pre-harvest, and during harvest • At steps in a process where materials, including water, are added where potential microbial ingress could occur • During process purification steps, taking into account factors like the sample container, sample port location, and precautions for aseptic technique and gowning • Immediately prior to steps for bioburden reduction or sterilization"	PDA recommends clarifying product in the 2nd bullet as current language states nonsterile product which is not in scope of this chapter. Additionally, PDA suggests adding examples for the 3rd bullet to assist the reader.	*Table 1. Considerations for Bioburden Sampling* <u>Topic: Sample **point**</u> "Define where in the manufacturing and/or operational processes samples are taken as determined through a risk assessment. Examples of sampling **points** include but are not limited to: • Following cleaning and clean hold times for product-contact equipment • Prior to filling a primary container for a **low bioburden bulk** product • During different stages of biologics manufacturing, such as bioreactor media, end-of-production pre-harvest, and during harvest. **For example, bioburden monitoring of process steps where material is held for a period of time under conditions conducive for microbial survival and/or proliferation.** • At steps in a process where materials, including water, are added where potential microbial ingress could occur • During process purification steps, taking into account factors like the sample	Prevent potential confusion of referencing material/product not within scope of the chapter, i.e., nonsterile product. Provides guidance on selection of manufacturing stages to be monitored for bioburden.

Section: Bioburden Sampling			
Current Text	**Comment to Text**	**Proposed Change**	**Rationale for Change**
		container, sample port location, and precautions for aseptic technique and gowning • Immediately prior to steps for bioburden reduction or sterilization"	
Table 1. Considerations for Bioburden Sampling <u>Topic: Sample storage conditions</u> "Define storage conditions that samples may be held in prior to testing. Storage conditions (temperature, location) must be defined. Storage beyond 2°–8° at 24 h would be permissible with appropriate justification and qualification. *See Microbiological Best Laboratory Practices ⟨1117⟩.*"	PDA recommends rewriting statement to clarify intent for the reader by referring to the storage time followed by temperature conditions.	*Table 1. Considerations for Bioburden Sampling* <u>Topic: Sample storage conditions</u> "Define storage conditions that samples may be held in prior to testing. Storage conditions (temperature, location) must be defined. Storage beyond **24 h at 2°–8°** would be permissible with appropriate justification and qualification. *See Microbiological Best Laboratory Practices ⟨1117⟩.*"	Recommended wording focuses the reader back to the time requirement followed by the appropriate temperature conditions to avoid potential misinterpretation of expectations.

Section: Bioburden Test Method			
Current Text	**Comment to Text**	**Proposed Change**	**Rationale for Change**
"If the total aerobic microbial count method cannot detect the anticipated bioburden, different nutrient culture media, incubation conditions, and growth promotion may be applied and justified in the bioburden test User Requirements."	PDA proposes aligning wording in the text and the table to make intent clearer.	"If the total aerobic microbial count method cannot detect the anticipated bioburden, different nutrient culture media, incubation conditions, and growth promotion **should be** applied and justified in the bioburden test User Requirements."	Aligning the language removes any potential reader misunderstanding due to assuming word choice was intentionally designed to convey the level of requirement; "may" verses "should".

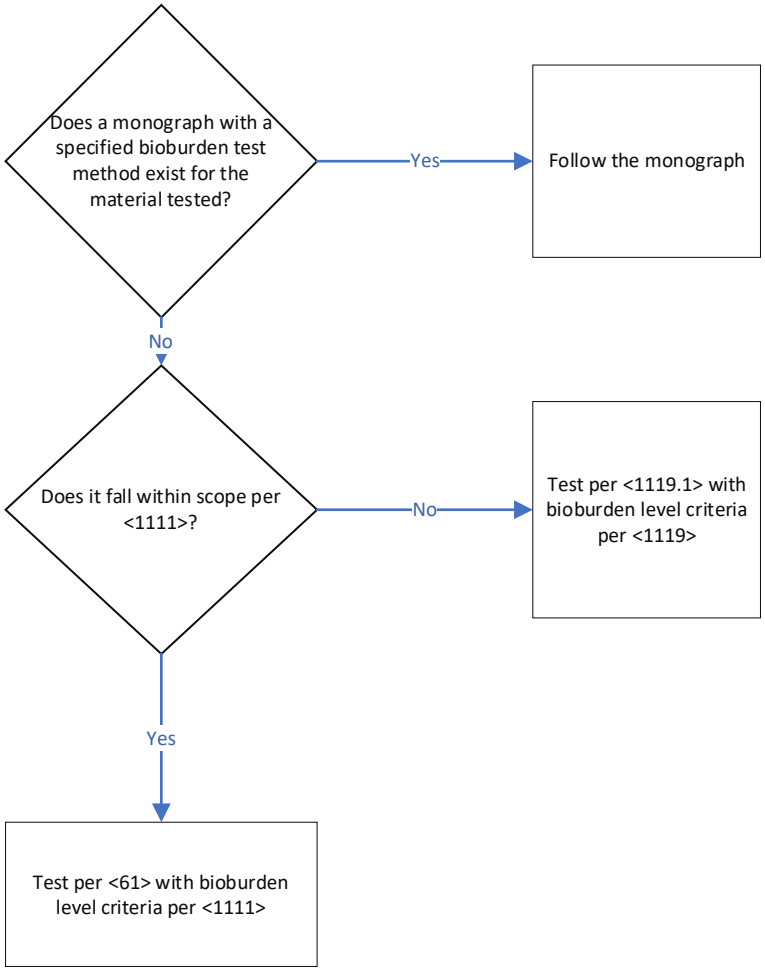
Section: Bioburden Test Method			
Current Text	**Comment to Text**	**Proposed Change**	**Rationale for Change**
Table 2. Considerations for Bioburden Test User Requirements Topic: Acceptance Criteria "Table 3 lists recommended bioburden limits for a range of sample types. A user should document the required bioburden limit and ensure that the amount of sample tested is sufficient to demonstrate conformance. Alternative sample amounts may be acceptable when justified and supported by statistical analysis. For an example, see Yang et al., 2015 (4)."	PDA recommends aligning wording in Table 2 to the Section *Assessment of Bioburden Monitoring* to make intent clearer.	*Table 2. Considerations for Bioburden Test User Requirements* Topic: **Bioburden Level** "Table 3 lists recommended bioburden **level** for a range of sample types. A user should document the **established** bioburden **level** and ensure that the amount of sample tested is sufficient to demonstrate conformance. Alternative sample amounts may be acceptable when justified and supported by statistical analysis. For an example, see Yang et al., 2015 (4)."	In the Chapter Section *Assessment of Bioburden Monitoring* it states "All sample types must have established, documented, and justified microbiological quality attributes related to both the number and the nature of the recovered organisms; Table 3 provides recommendations." By changing the language in Table 2 to align with the language in the Section Assessment of Bioburden Monitoring, it makes the statement clearer and creates a link for the reader due to the alignment of the wording.

Section: Assessment of Bioburden Monitoring			
Current Text	**Comment to Text**	**Proposed Change**	**Rationale for Change**
"All sample types must have established, documented, and justified microbiological quality attributes related to both the number and the nature of the recovered organisms; Table 3 provides recommendations."	PDA suggests providing the reader guidance on how to determine what is an acceptable microbial load (for raw materials, for in-process products).	"All sample types must have established, documented, and justified microbiological quality attributes related to both the number and the nature of the recovered organisms. **Setting bioburden levels should be performed through a risk-based assessment, taking into consideration whether a raw material or processing step can harbor or allow for the proliferation of microorganisms. Considerations should also be given to subsequent processing stages; e.g., bio-reduction or sterilization steps in support of establishment of risk-based bioburden levels.** Table 3 provides recommendations."	Provides the reader with a list of factors to consider during the selection of acceptable bioburden levels.
"In addition, an assessment of recovered species must be completed to determine if they represent a loss of control, risk to product quality, or patient risk."	PDA suggests providing clarity for the handling of recovered organism data. Specifically, PDA recommends changing the wording to indicate trending to align with the chapter scope of bioburden monitoring.	"In addition, **recovered bioburden should be fully assessed and trended** to determine if they represent a loss of control, risk to product quality, or patient risk.**"**	Clarifying wording to reflect the need to perform trending of the organisms recovered.
"Trending analysis through the use of control charts should be used to evaluate the bioburden of the process and to identify the occurrence of adverse trends."	PDA recommends removing the specificity of "control charts" and use more general language of "appropriate tools".	"Trending analysis **using appropriate tools** should be conducted to evaluate the bioburden of the process and to identify the occurrence of adverse trends."	There are many different tools that can be used for bioburden trending and control charts may not be the most appropriate based on bioburden data not being conducive for this tool.

Section: Assessment of Bioburden Monitoring			
Current Text	**Comment to Text**	**Proposed Change**	**Rationale for Change**
Table 3. Recommended Bioburden Limits Sample Type: Purified drug substance "≤1 CFU/10 mL"	PDA recommends changing the recommended bioburden level. Based on the sample type description, PDA interprets the "Purified Drug Substance" to be the purified bulk drug substance, which is upstream of the drug substance final filtration step, for which the proposed limits are more appropriate.	*Table 3. Recommended Bioburden Limits* **Bioburden Level**: "**≤10 CFU/10 mL**"	Updated recommended bioburden level aligns with the expectation of this sample being an in-process sample point for a low-bioburden drug substance and being taken prior to the final bio-reduction step.
Table 3. Recommended Bioburden Limits Sample Type: Ready-to-sterilize components (RTS) "≤100 CFU/per stated sample size tested"	PDA proposes removal of this line item.	**Remove line item for "Ready-to-sterilize components (RTS)".**	There are many different types of sterilization processes that can be used with the type of bioburden monitoring along with bioburden level being dependent on the sterilization process. Additionally, specific guidance is provided in other spaces based on sterilization process.
Table 3. Recommended Bioburden Limits Sample Type: Pre-bioburden reducing filter for drug product "≤10 CFU/100 mL"	PDA recommends changing the name of the sample type to clarify to the reader the point in the process where the sample is collected. Also, PDA suggests changing the recommended bioburden level as it is currently set at the same bioburden level for samples collected prior to final sterilizing filter.	*Table 3. Recommended Bioburden Limits* Sample Type: "**Bulk solution prior to primary filtration."** **Bioburden Level**: "**Bioburden level should be established based on process capabilities.**"	Provides clarity to the reader on the sample point. Updated recommended bioburden level aligns with the expectation for reduction in microbial levels between samples taken prior to a bio-reduction step and samples taken after the step.
Table 3. Recommended Bioburden Limits Sample Type: Presterilizing filter for drug product	PDA recommends changing the name of the sample type to clarify intent for reader.	*Table 3. Recommended Bioburden Limits* Sample Type: **Bulk solution prior to final sterile filtration**	Revised language clarifies where the sample is taken and aligns with language used in other industry guidance documents (e.g., Annex 1).

Section: Assessment of Bioburden Monitoring			
Current Text	**Comment to Text**	**Proposed Change**	**Rationale for Change**
Table 3. Recommended Bioburden Limits Pre-Terminal Sterilization (moist heat or heat)	PDA recommends removing the "or heat" It is unclear as to the intent of the "or heat" as outside of dry heat other forms of heat sterilization would be categorized as moist heat.	Pre-Terminal Sterilization **(moist heat)**	It is unclear what methods are covered under the term "heat"; terminology aligns with EMA 2019 sterilization guide.

Section: Appendix			
Current Text	**Comment to Text**	**Proposed Change**	**Rationale for Change**
Figure 1. Determining method and acceptance criteria for quantification of microorganisms.	PDA proposes to adopt an updated version of Figure 1.	Please see image below.	Updated figure provides more clarification for reader on how to utilize USP guidance. By streamlining the figure, it will give readers more direction on which Chapter will provide the guidance needed.


Does a monograph with a specified bioburden test method exist for the material tested?
Yes
Follow the monograph
No
Does it fall within scope per <1111>?
No
Test per <1119.1> with bioburden level criteria per <1119>
Yes
Test per <61> with bioburden level criteria per <1111>