October 13th, 2016

Bethesda Towers
4350 East West Highway, Ste 600
Bethesda, MD 20814 USA
Tel: +1 (301) 656-5900
Fax: +1 (301) 986-0296
www.pda.org

PDA Europe gGmbH
Am Borsigturm 60
13507 Berlin
Germany

European Medicines Agency
30 Churchill Place Canary Wharf
London E14 5EU United Kingdom

Ref: EMA/CHMP/CVMP/QWP/BWP/850374/2015
Guideline on the sterilization of the medicinal product, active substance, excipient, and primary container

Dear Sir/Madam,

PDA appreciates the opportunity to comment on this draft guideline and supports both aseptic and terminal sterilisation approaches being included.

Based on the documented, successful, safe application of aseptic processing for many years, there is a lack of scientific and risk-based evidence to support the need for application of terminal sterilization or other lethal treatment processes in well -designed, properly controlled and operated aseptic processes. Accordingly, PDA believes that aseptic manufacture in these cases can provide products of suitable quality there should be no expectation that products produced through aseptic manufacture would need the addition of some moderated 'terminal sterilisation' or other lethal treatment conditions. However, where there is interest in reducing the ongoing testing requirements (i.e., bioburden testing, environmental monitoring or media fills), post-aseptic processing lethal treatment options up to and including traditional terminal sterilization using moist heat or an alternate technology should be considered.

PDA has provided specific examples within the comment matrix where our members feel additional clarification and detail would reduce potential misinterpretations by those using this guidance and has identified those recommendations considered by PDA to be the most critical aspects of the draft to be remedied.

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 were prepared by a committee of experts with experience in pharmaceutical and biological manufacturing including members representing the Science Advisory Board, Process Validation and Aseptic Processing Task Forces, and multiple subject matter experts from within our Interest Group leadership.

If there are any questions, please do not hesitate to contact me.
Sincerely,

Georg Roessling, Vice President, PDA Europe

Cc: Richard Johnson, PDA; Denyse Baker, PDA; Rich Levy, PDA.

<13 Oct 2016>

Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container

Comments from:

Parenteral Drug Association (PDA)

Please note that these comments and the identity of the sender will be published unless a specific justified objection is received.

When completed, this form should be sent to the European Medicines Agency electronically, in Word format (not PDF).

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8416
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)		Outcome (if applicable) *(To be completed by the Agency)*
	PDA supports both aseptic and terminal sterilisation approaches being included in the guidance. Based on the documented, successful, safe application of aseptic processing for many years, there is a lack of scientific and risk-based evidence to support the need for application of terminal sterilization or other lethal treatment processes in well designed, properly controlled and operated aseptic processes. Accordingly, PDA believes that aseptic manufacture in these cases can provide products of suitable quality and there should be no expectation that products produced through aseptic manufacture would need the addition of some moderated 'terminal sterilisation' or other lethal treatment conditions. However, where there is interest in reducing the ongoing testing requirements (i.e., bioburden testing, environmental monitoring or media fills), post-aseptic processing lethal treatment options up to and including traditional terminal sterilization using moist heat or an alternate technology should be considered.	**Y**	
	Comments on $F_0 \geq 8$ Minutes Mandate for Terminal Moist Heat Sterilization Processes An inconsistent position is presented in this document regarding the preference of terminal sterilization processes over aseptic processing. The document states that "terminal sterilization is preferred to sterilization by	**Y**	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)		Outcome (if applicable) *(To be completed by the Agency)*
	filtration and/or aseptic processing because it provides a sterility assurance level (SAL) that is possible to calculate, validate and control…" (Lines 53-55). However, there are sections (Lines 133 and 388) in this document where $F_0 \geq 8$ minutes is mandated for terminal moist heat sterilization processes. If the heat history associated with this minimum physical lethality ($F_0 \geq 8$ minutes) cannot be tolerated by the product, then aseptic processing is the required approach and this fails to recognize the scientific validity and associated historical and successful use of moist heat sterilization processes which operate at $F_0 < 8$ minutes with capability to provide a product SAL $\leq 10^{-6}$. From a patient risk perspective, terminal moist heat sterilization processes that operate at $F_0 < 8$ minutes and deliver an SAL of $\leq 10^{-6}$ represent a risk level that is significantly lower than filter sterilization and/or aseptic processing. In support of these lower process F_0 values and their associated ability to provide a $\leq 10^{-6}$ SAL, the following example of an application of the Product Specific Approach (i.e., Combined Bioburden/BI Approach) taken from PDA Technical Report No. 1 (2007 Revision – Page 27) must be considered: <u>Example 1</u> a) Bioburden testing of product $N_0 <$ 10^1 resistant microorganisms per unit of product. $D_{121°C} <$ 0.25 minutes		

Stakeholder number *(To be completed by the Agency)*	General comment (if any)		Outcome (if applicable) *(To be completed by the Agency)*
	b) values used for process design N_0 = 10^2 microorganisms N_F = 10^{-6} (PNSU) $D_{121°C}$ = 0.4 minutes c) calculated minimum lethality to achieve a PNSU of less than 10^{-6} $F_{121°C}$ = $(Log\ N_o - Log\ N_F) \times D_T$ (Log 10^2 - Log 10^{-6}) x 0.4 minute = **3.2 minutes** **An SAL or PNSU of 10^{-6} is achieved in this example with a physical lethality of 3.2 minutes for a product bioburden of 10^2 spores with a $D_{121°C}$ value of 0.4 minutes.** It should be noted that ongoing bioburden monitoring (i.e. population and resistance) should be performed for sterilization processes developed with this approach. The estimate of bioburden population and resistance used in this example is considered extremely conservative when compared to the much lower population and heat resistance for the bioburden in products manufactured under typical pharmaceutical GMP controls used for terminally sterilized products. Additionally, it is possible that even lower physical lethality requirements may also be scientifically supported with proper control over bioburden. Examples of the use of F_0 < 8 minutes for terminal moist heat sterilization		

Stakeholder number *(To be completed by the Agency)*	General comment (if any)		Outcome (if applicable) *(To be completed by the Agency)*

processes can be further confirmed in the literature and based on commentary from Regulators in the public forum. For example, Pflug and Evans (2000) *(Carrying Out Biological Qualification, the Control Operation of Moist-Heat (Steam Sterilization) Processes for Producing Sterile Pharmaceutical and Medical Devices, PDA J Pharm Sci and Tech 2000, 54 117-135.)* determined that a sterilization process with an F_0 of 1.75 minutes was capable of achieving a 10^{-6} SAL for a liquid pharmaceutical product that contained 10 spores with a D_{121C}value of 0.25 minutes. Additionally, moist heat sterilization processes with F_0 values of less than 8 minutes are in widespread use in Japan-see Table 1.

Table 1 taken from Roundtable on Parametric Release published in Pharmaceutical and Medical Device Regulatory Science Society of Japan, Vol. 46, No. 9, pp 572-588, 2015.

Table1; Sterilization (F_0) to the intravenous solution product in Japan (Total number of units produced by 13 manufacturers during 2005 – 2010)

F_0 value range (Minutes)	Accumulated number of manufactured units	%
≥ 8	7,090,000	0.2
4 to < 8	15,189,750	0.5
2 to <4	569,348,566	19.9
< 2	2,272,129,587	79.3

From the survey by The Intravenous Solution Society

2. Specific comments on text

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Critical Comments	Outcome *(To be completed by the Agency)*
Exact Line # (s)	Name (First & Last)	Comment: Proposed change (if any):		
72		Comment: The GMP certificate for API is not mandatory in Europe. See also comments to line 286-301. Proposed Change: Only the information expected in a quality dossier, ~~including information on the need for Good Manufacturing Practice (GMP) certificates,~~ is described. General GMP requirements are not included.	**Y**	
74-76		Comment: Restricting terminal sterilization to the conditions listed in Ph. Eur 5.1.1 is overly restrictive and actually precludes the expanded use of terminal sterilization which is the clear preference of EMA (see Lines 57 and 58). A simplification of the sentence maintains the intent of expanding the use of terminal sterilization by removing the artificial constraints that are imposed. Proposed change (if any): Terminal sterilisation by heat and ionising irradiation to achieve an SAL of $\leq 10^{-6}$, sterilisation by filtration and aseptic processing are considered.	**Y**	
107		Comment: The statement regarding SAL is mathematically	**Y**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Critical Comments	Outcome *(To be completed by the Agency)*
		imprecise and must be improved with the use of "≤". This comment applies to this entire document in all cases where "SAL of 10^{-6} or better" is used. Proposed change (if any): "…demonstration of a SAL ~~of ≤~~10^{-6} ~~or better"~~		
120		Comment: The operating conditions used in the actual process are also of importance to the validation. Proposed Change: "the solution to be filtered **and process conditions** should be used in the validation unless justified."	**Y**	
133; also 150-151		Comment: This statement contradicts the following statement from Line 57: "Therefore, terminal sterilisation provides the highest assurance of sterility and should be used whenever possible." This statement precludes the use of terminal sterilization processes where F_0 is less than 8 minutes even though these processes are capable of providing and ≤10^{-6} SAL and have been successfully utilized for many years. Also, the term "moist heat" should be used in place of "steam" (implies saturated steam) as there are terminal sterilization processes available and in common use (e.g., air overpressure water spray) that are not true saturated steam processes. Proposed change (if any): "**An SAL ≤ 10^{-6}** ~~F_0 ≥ 8 minutes~~ is required for all ~~steam~~ **moist heat** sterilisation processes."	**Y**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Critical Comments	Outcome *(To be completed by the Agency)*
140 - 141		**Comment: It is only the heat resistant or spore bioburden that potentially represent a challenge to the moist heat sterilization process.** **From: As is** **Proposed change (if any): *"For terminal sterilisation using a reference condition of the Ph. Eur. 5.1.1, (≥121 °C, ≥15 min in all units), validation data for the sterilisation cycle is not required. In all other cases physical and biological validation of the sterilization cycle should be provided to demonstrate a SAL of 10^{-6} or better, as described in PH. Er. 5.1.1. The SAL of such sterilization process should be calculated from the maximum number of heat resistant or spore bioburden per container."***	**Y**	
145-149, see also comment to lines 158-161		Comment: As written with the stated limitation on exposure or hold time temperatures, this text restricts the use of terminal sterilization rather than expanding its use which PDA believes to be the more appropriate intent. A sterilization process must predictably and reproducibly destroy the bioburden present to an acceptable level of probability; and with the use of the F_0 concept and biological indicators, this is scientifically valid at temperatures ≤ 115°C. Also, the requirement for bioburden population and testing should be based whether or not the Overkill Design approach was used as the use of this approach is possible, although much longer exposure times are required, at	**Y**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Critical Comments	Outcome *(To be completed by the Agency)*
		temperatures ≤ 115°C.. Proposed change (if any): Delete this section.		
150 and 151 (see also 120)		Comment: Statement is mathematically incorrect; SAL requirements are always expressed as "less than" or "less than or equal to". Proposed change (if any): "…demonstrate that a SAL ~~≤of not less than~~ 10^{-6}"	**Y**	
158 to 161, see also comments to line 145-149		Comment: The validity of sterilization processes at 115ºC and below is not enhanced through the use of incremental requirements for justification of sterilisation start time or through the use of several relevant biological indicators. The use of "several relevant biological indicators" is scientifically unnecessary if using an overkill biological indicator such as *Geobacillus stearothermophilus* or a biological indicator that models product bioburden with the Product Specific Approach. Proposed change (if any): Delete section.	**Y**	
165 - 167 And 189		Comment: What is the scientific justification for the maximum bioburden limit of 100 CFU/100mL? Proposed change (if any): Recommend deletion of this limit or modification to require that the bioburden limit should be consistent with the population of moist heat resistant spores	**Y**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Critical Comments	Outcome *(To be completed by the Agency)*
		used in SAL calculations.		
219		Comment: Parametric release is not permitted by this statement and product sterility testing is not recognized as a release requirement in ISO11135:2014 Parametric Release Definition 3.2.5 and Section 11.1 for product release criteria Proposed change (if any):"The effectiveness of the process should be routinely checked for every product batch using a suitable biological indicator ~~and by product sterility testing~~. **unless parametric release has been approved**."		
233-235		Comment: It is necessary to accurately and completely specify the filtration system and its components. The original text is ambiguous. Proposed change (if any): " ~~The type and number of sterilising filters, filter area, material and nominal pore size should be described~~ "**For each product and batch size thereof, the catalogue number and number of each sterilising filter should be specified**. ~~together with a description of the filter integrity testing.~~ **The filter integrity test procedure(s) should be specified** (principle of the test and details when the tests are performed including the test limits ~~before and after filtration~~).		

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Critical Comments	Outcome *(To be completed by the Agency)*
235-236		Comment: The choice whether a filter is integrity tested before use and after the sterilization of the filter should be based upon risk assessment and be kept as a decision by the filter user. There is no description of what "specifically justified and validated" means, which will result in confusion and multiple ways of interpretation. Proposed change (if any): ~~The integrity of the sterilised filter should be verified before use but after its sterilisation unless specifically justified and validated, and should be confirmed immediately after use~~. **The necessity of a pre-use post-sterile integrity test of a filter should be determined by a risk assessment process.**	**Y**	
240 - 243		Comment: Pre-sterilising filter or pre-filtration can be misinterpreted. Proposed change (if any): If ~~a pre-sterilising~~ **an additional** filter is installed, the filter closest to the filling …. The sampling for bioburden testing may be performed prior to ~~the pre-filtration~~ **the additional filter**, provided that no hold time is scheduled …"		
244 -		Comment: In PDA's opinion the limit of 10 CFU/100 ml is not	**Y**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Critical Comments	Outcome *(To be completed by the Agency)*
250		scientifically justified in all cases and recommends instead to require an understanding of bioburden (source, nature, concentration), robustness in the removal process, and impact on quality. Proposed change (if any): Delete this section and replace as indicated. **Sterilising filtration must be validated to demonstrate complete removal of bioburden organisms under process conditions. Bioburden levels in front of the sterilising grade filter shall not exceed the validated limits. If necessary, additional filters can be used in front of the terminal sterilising grade filter to reduce the bioburden to an acceptable level. This reduction has to be tested and documented.**		
250		Comment: The 100 ml sample size may be valid for the microbial filtration test method, but other technologies allow smaller sample volumes. Proposed change (if any): "Bioburden should be tested in a product sample of 100 ml in order to ensure the sensitivity of the method. **Smaller volumes may be used when justified.**"		

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Critical Comments	Outcome *(To be completed by the Agency)*
253-256		Comment: Text revised for clarification. Proposed change (if any): Change to read: "**In addition to microbial retention, filter validation data should include** bacterial retention capacity, solution compatibility and leachable filter materials. The solution to be filtered should be used in the validation unless justified, **for example when the solution is hostile to the challenge organism**. ~~(for instance when the pre-filtration integrity test is performed using water for injections during routine production)~~.		
257-264		Comment: PDA proposes the following changes for clarification. Proposed change (if any): "If a sterilising filter is used for more than one working day or is re-used for additional batches, the total filtration time and the number of batches the filter is used for should be stated ~~and justified~~ **and the filtration process validated to show performance robustness**. If re-used, the filter should be dedicated to ~~a single~~ **one** product, **thoroughly cleaned and** sterilised before re-use. **The cleaning and sterilization of the filter must be validated. The process validation of the filter should include bacteria retention studies with the product or a challenge fluid as close to the product composition as**		

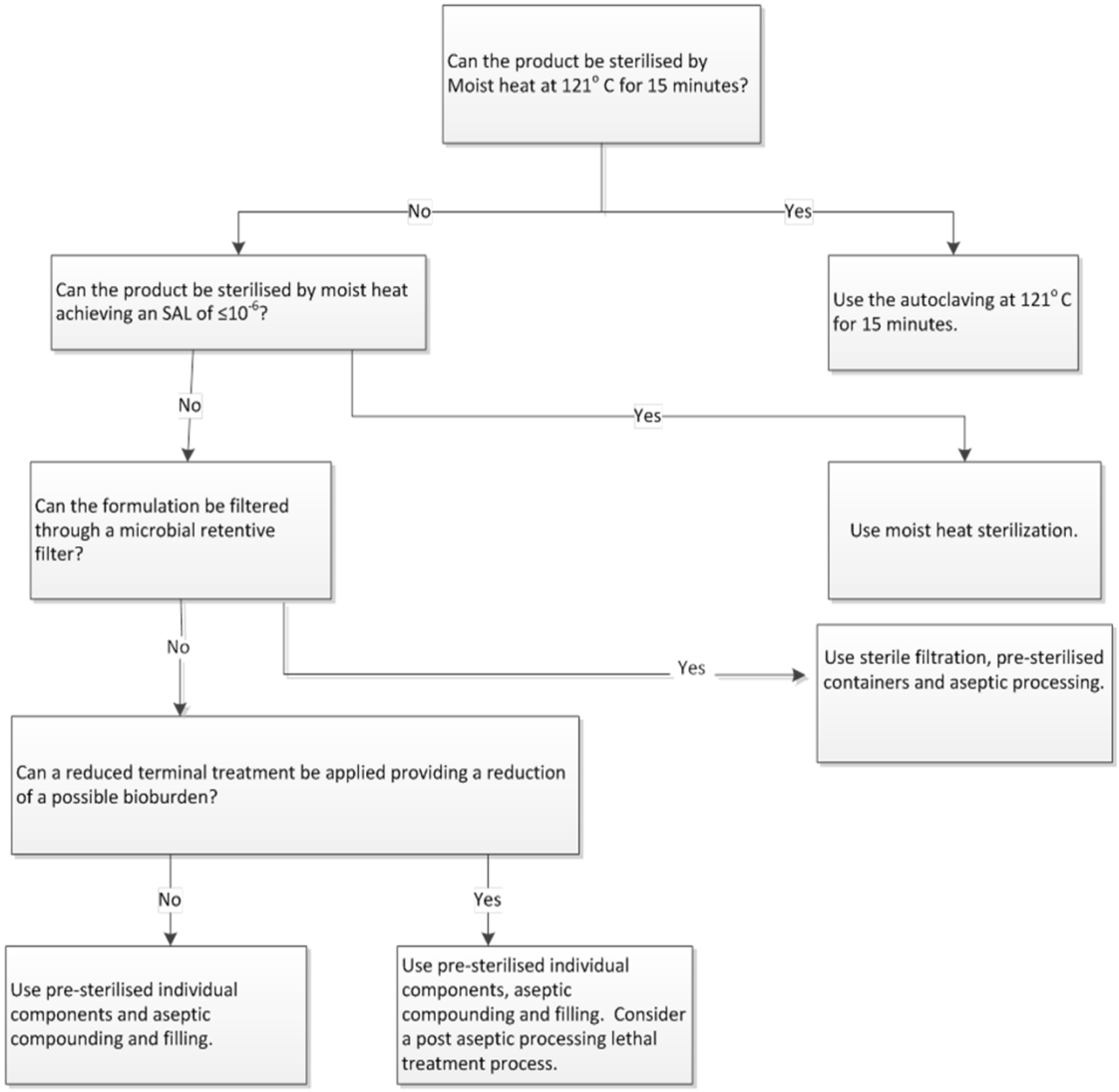
Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Critical Comments	Outcome *(To be completed by the Agency)*
		possible using the actual operating parameters. The validation study should encompass the maximum filtration, cleaning and sterilization cycles the filter is subjected to.		
286-301		Comment: As written, this section is confusing and seems to require more than GMPs. GMP inspection is not mandatory for active substance manufacturer. Proposed Change: Suggest using exactly the text from the current GMPs or providing reference to specific current GMP sections.		
39, 106, 328 – 333, 381, 385, glossary,		Comment: This introduces the use of an undefined "terminal microbial reduction' process. It would be preferable to expand the use of terminal sterilization to conditions where the bioburden can be reproducibly destroyed. A terminal sterilization process is understood as one that inactivates the bioburden present to a SAL of≤ 10^{-6}. Cycles that follow aseptic processing may not require the same time-temperature conditions as those performed without preceding aseptic fill to achieve the required SAL. In PDA's experience, these are still effective and safe sterilization processes. Proposed change (if any): Replace 'terminal microbial reduction' with 'post aseptic processing lethal treatment' throughout the document. Add to glossary with the following definition: the	**Y**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Critical Comments	Outcome *(To be completed by the Agency)*
		application of a terminal treatment (e.g., heat or other technology) capable of inactivating specified microorganisms. For example, this treatment could range from the application of a mild treatment that is capable of inactivating only vegetative organisms through application of classical sterilization treatment which is capable inactivating all heat resistant spores while supporting a 10^{-6} SAL		
380-382		Comment: Delete 380-382--this section based on the following presented above: Based on the well-documented successful and safe application of aseptic processing for many years, there is no scientific or risk-based justification for the need for the application of a terminal sterilization or other lethal treatment process after aseptic processing. Accordingly, PDA continues to contend that aseptic manufacture alone CAN provide products of suitable quality and there should be no expectation that products produced through aseptic manufacture would need the addition of some moderated 'terminal sterilisation' or other lethal treatment conditions.	**Y**	
388 Decision Tree; aqueous products		Comment: PDA recommends the diagram be modified as indicated below **(see attached Decision Tree)** based on the rationale presented for Lines 380-383 above. Additionally, the use of heat treatment should be broadened to include treatment technologies capable of microbiological inactivation besides heat.	**Y**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Critical Comments	Outcome *(To be completed by the Agency)*
		Proposed change (if any): Please clarify.		
391		Comment: PDA recommends the diagram be modified as indicated below **(see attached Decision Tree)** based on the rationale presented for Lines 380-383 above. The current decision tree allows the adoption of a 25 kGy sterilizing dose without the requirement for proper validation. PDA recommends adding the requirement to validate <u>all</u> radiation doses per ISO11137. Additionally, the use of heat treatment should be broadened to include treatment technologies capable of microbiological inactivation besides heat	**Y**	
SAL Definition		Comment: PDA recommends use of the definition from ISO 11137 "Probability of a viable microorganism being present on a product unit after sterilization."		
SAL Definition		Comment: The SAL mathematical description is incorrect. Proposed change (if any): From: "An SAL of 10^{-6}, for example, denotes a probability of not more than one viable micro-organism in 1×10^{6} sterilised items of the final product." To: "An SAL of $\leq 10^{-6}$, for example, denotes a probability of not more than one viable micro-organism in 1×10^{6} sterilised items of the final product."	**Y**	

Line number(s) of the relevant text *(e.g. Lines 20-23)*	Stakeholder number *(To be completed by the Agency)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	Critical Comments	Outcome *(To be completed by the Agency)*
Sterility Definition		Comment: Survival probability is not determined by organism type (resistance covers this) and environment during treatment. PDA recommends the ISO Definition be used or the guideline definition be modified to conform based on the recommendation below. Proposed Change (if any): For a given process, the probability of survival is determined by the number~~, types~~ and resistance of the micro-organisms present and by ~~the environment in which the organisms exist~~ **level of lethal stress (e.g., F_0, kGy, etc.) to which the organisms are exposed to** during treatment. Or the ISO definition: 2.45 Sterility - state of being free from viable microorganisms. Reference ISO 11139: 2006. NOTE In practice, no such absolute statement regarding the absence of microorganisms can be proven.		
Sterilisation		Comment: PDA recommends the following definition from ISO 11135: 2014 Definition 3.47 because it is a more comprehensive definition. Proposed Change: ~~A process that inactivates or removes viable micro-organisms in a product until sterility is obtained.~~ "Validated process used to render a product free of all forms of viable microorganisms"		

Decision tree for sterilisation choices for aqueous products



Decision tree for sterilisation choices for non-aqueous liquid, semi-solid or dry powder products