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September 25, 2015

European Directorate for the Quality of Medicines and Healthcare
Council of Europe
7 allée Kastner
CS 30026, F-67081
Strasbourg, France

Re: 5.1.2. *Biological indicators and related Microbial Preparations use in the Manufacture of Sterile Products and Indicators for Depyrogenation Processes*
Reference number: PA/PH/Exp. 1/T (10) 4 ANP Text number: 50102
Group 1 Issue 27.3 Deadline 30 .09. 2015

Dear Sir/Madam,

PDA encourages Ph. Eur. to continue to work towards harmonized concepts globally with other Health authorities such as the existing and planned ISO framework especially ISO 11139. PDA has concerns with the proposed changes to this chapter and the inclusion of such diverse topics as filter validation, endotoxin challenges and sterilization cycle development. PDA has a concern that some of the important guidance in this chapter could be overlooked when too many topics are combined and therefore recommends that this chapter be specifically focused on biological indicators and that even the original title be only slightly modified to *Evaluation* of Biological Indicators for Sterilisation.

PDA recommends harmonization of definitions and concepts wherever possible to avoid the possibility of conflicting requirements as well as duplication of effort for users globally. In the case of biological indicators, ISO has a well-recognized definition which PDA recommends for adoption in this standard.

As currently written, the draft chapter addresses Biological Indicators including challenges such as endotoxin and microbial suspensions for filter validation. Typically, these types of challenges are not considered BIs by industry and endotoxin is not viable therefore does not meet the definition. While the filter challenge meets the strict definition, PDA believes it is a different sterilization process (removal rather than kill) and the challenge does not involve lethality (D / z / F_{BIO} values) but only population counts. PDA thinks this could lead to confusion in understanding and application of the chapter. We are concerned that

some of the important guidance in this chapter could be overlooked when too many topics are combined and recommends focussing on biological indicators for lethality based sterilization processes only.

PDA welcomes pharmacopeial involvement on diverse topics such as filter validation, endotoxin challenges and sterilization cycle development but feels the nature, risks and controls associated with each of these challenges are sufficiently different to warrant their own chapters or reference to other existing standards. Other General Chapters that might be better suited for these topics include: 5.1.5. APPLICATIONS OF THE F_0 CONCEPT TO STEAM STERILIZATION OF AQUEOUS PREPARTIONS and 5.1.1. METHODS OF PREPARATION OF ASEPTIC PRODUCTS.

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 microbiology and sterilisation experts representing our Science Advisory Board and Board of Directors.

If you have further questions, please do not hesitate to contact me (Johnson@pda.org) or Georg Roessling, Ph.D. Senior Vice President, PDA Europe, (Roessling@pda.org).

Sincerely,

Richard M. Johnson

Richard M. Johnson
President, PDA

Cc: Georg Roessling, PDA, Denyse Baker, PDA
Attachment

5.1.2. Biological indicators and related Microbial Preparations use in the Manufacture of Sterile Products and Indicators for Depyrogenation Processes

Reference number: PA/PH/Exp. 1/T (10) 4 ANP Text number: 50102
Group 1 Issue 27.3 Deadline 30 .09. 2015

Comments from:

Parenteral Drug Association

1. General comments

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
Name	Comment	Decision to Submit/ withdraw comment
	PDA recommends harmonization of definitions and concepts wherever possible to avoid the possibility of conflicting requirements as well as duplication of effort for users globally. In the case of biological indicators, ISO has a well-recognized definition which PDA recommends for adoption in this standard. The definition of BI in ISO 11139 is: *Test system containing viable microorganisms providing defined resistance to a specified sterilization process.* As currently written, the draft chapter addresses Biological Indicators including challenges such as endotoxin and microbial suspensions for filter validation. Typically, these types of challenges are not considered BIs by industry and endotoxin is not viable therefore does not meet the definition. While the filter challenge meets the strict definition, PDA believes it is a different sterilization process (removal rather than kill) and the challenge does not involve lethality (D / z / F_{BIO} values) but only population counts. PDA thinks this could lead to	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	confusion in understanding and application of the chapter. We are concerned that some of the important guidance in this chapter could be overlooked when too many topics are combined and recommends focussing on biological indicators for lethality based sterilization processes only. PDA welcomes pharmacopeial involvement on diverse topics such as filter validation, endotoxin challenges and sterilization cycle development but feels the nature, risks and controls associated with each of these challenges are sufficiently different to warrant their own chapters or reference to other existing standards. Other General Chapters that might be better suited for these topics include: 5.1.5. APPLICATIONS OF THE F_O CONCEPT TO STEAM STERILIZATION OF AQUEOUS PREPARTIONS and 5.1.1. METHODS OF PREPARATION OF ASEPTIC PRODUCTS. Here are some examples: • 5.1.2. section 7 is *BIOLOGICAL INDICATORS FOR STERILISATION GRADE FILTRATION*. This is an uncommon use of the term biological indicator for describing the challenge organism for filter microbial retentivity testing (although it meets the strict ISO definition). Much of the information in this section overlaps with Ph. Eur. 5.1.1. Section *FILTRATION* and PDA recommends that all related information be included in that general chapter • The cycle validation section (moist heat area) seems out of scope. PDA recommends this would be more appropriate in a different monograph dealing with cycle validation. • In addition, there is little commonality between sterilization / BIs and endotoxin challenges which demonstrate Depyrogenation and are non-viable.	

Stakeholder number *(To be completed by the Agency)*	General comment (if any)	Outcome (if applicable) *(To be completed by the Agency)*
	This draft appears to have selected certain sections from the *paper: Biological Indicators, Tools to Verify the Effect of Sterilisation Processes* Position paper prepared on behalf of Group 1 (Biological Methods and Statistical Analysis) K. Haberer, H. van Doorne. without providing the context of the whole paper. For example this draft 5.1.2. chapter appears to be applying the concepts from paper which was based onBIs utilized steam sterilisation only,to all types of sterilisation. PDA feels greater clarity could be achieved by including additional information in General Chapter 5.1.5.	

2. Specific Comments

Section number(s) of the relevant text *(e.g. Lines 20-23)*	Contributed By *)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	**Outcome** Decision to Submit/ withdraw comment
Page 1, Lines 3-8		Comment: Consistent with the general comment above recommending focused focus on biological indicators, PDA recommends the title be similarly clear and proposes the original title be retained with only slight modification. Proposed change : **Evaluation and Use of** Biological Indicators for **Decontamination**	
Page 1, Line 16-17		Comment: PDA disagrees with the premise that BIs are not to be employed for routine monitoring. In PDA's experience, and as found in ISO 11135, chapter 11, using BIs can be a routine way to monitor the EO process if parametric release is not validated. Please refer to ISO 11135-1 (2014) Section 11.1(b). Proposed change: *that BIs are in most cases only to be used for development of the sterilisation process.* Alternate Proposed Change: Add the following, *and not for routine monitoring* **unless otherwise stated in this chapter**.	
Page 1, Line 45 - 46		Comment: In PDA's opinion, this creates a new application and broadens the use of biological indicators by including challenge organisms that are used to validate sterilisation grade filtration which is not a kill / lethality based sterilization process. Therefore this concept and the corresponding section should not be included in this general chapter.	

Section number(s) of the relevant text *(e.g. Lines 20-23)*	Contributed By *)*	Comment and rationale; proposed changes *(If changes to the wording are suggested, they should be highlighted using 'track changes')*	**Outcome** Decision to Submit/ withdraw comment
		Proposed Change: See general comments	
Page 2 Line 10:		Comment: Because filter sterilization is not a terminal sterilization process, PDA recommends removing the term units. Proposed change: "non-terminal units…" to non-terminal sterilization **processes** …"	
Page 2: Line 1-20,		Comment: Depending upon the cycle design approach, the BI and the F_{BIO} delivered, survivors may be expected and the process will still be fully capable of supporting a 10^{-6} SAL. See PDA Technical Report 1 *Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control.* PDA recommends adding the text as shown below to clarify situations when surviving micro-organisms are acceptable. Proposed Change: …*However, when a full sterilisation process* **with overkill cycles** *is used, there will typically be no surviving viable micro-organisms.* **Even with an overkill cycle, there may be occasional survivors which can be scientifically justified if the required SAL is achieved.**	
Page 2: Line 28-34		Comment: PDA recommends that this section be deleted because it is out of scope. The focus should remain on spores for the validation of terminal lethality based sterilisation processes. Proposed Change: See general comments	
Page 3: Line 9,		Comment: PDA recommends that product specific conditions in	

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and Lines 11-12		addition to load specific conditions be evaluated in determining the most difficult position to sterilise. Proposed Changes: In the development of a sterilisation process, the load **and product** should be assessed… …When choosing the optimum biological challenge to a sterilisation process, the conditions in the most difficult position to sterilise in the load **and product** should be simulated as closely as possible.	
Page 3 line 18		Comment: PDA recommends this section applies to any kill based sterilization cycle and not just to terminal sterilisation and the heading should be modified. The same principles should be followed for non- terminally kill based, sterilized items such as equipment used in aseptic processing. If the validation of filters (removal rather than kill) is deleted from the chapter, see general comment, the word "terminal" can be deleted from the section title eliminating potential confusion regarding terminal sterilization and aseptic processing Proposed Change: 2-1. *DESCRIPTION OF BIOLOGICAL INDICATORS FOR STERILISATION PROCESSES*	
Page 3: Lines 21-24		Comment: This section seems to imply that one can use a BI manufacturer, in the absence of a high level of confidence in that manufacturer's compliance to standards, by just confirming the labelled characteristics of their product. Without verifying a supplier's adherence to quality standards, the performance characteristics of the BI may not be homogenous across a lot or between lots, which invalidates testing to verify labelled	

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		characteristics. PDA recommends quality and other assessments as a base requirement for any BI supplier used, followed by confirmation of select label characteristics to confirm performance of a given lot. Proposed Change: PDA recommends deleting this sentence and adding a reference to section 2-2-2 for user requirements.	
Page 3 Line 30		Comment: PDA recommends the following clarification to avoid confusion to readers that all gas sterilization processes utilize this BI presentation. For example, EO universally is a paper strip. Proposed Change: …(e.g. strips of filter paper in glassine envelopes are frequently used for steam **and EO, while** *metal discs packaged in non-woven fibre envelopes* ***are used*** *for* ***hydrogen peroxide vapour(VHP).***	
Page 3 Line 31		Comment: Revise as shown for consistency: Proposed Change: *After exposure to the sterilisation process, the carrier is aseptically removed from the envelope* ***subjected to the appropriate recovery procedure, if applicable*** *and transferred to a suitable culture medium and incubated for a sufficient period of time at the appropriate temperature.*	
Page 4 Lines 11		*Comment: PDA recommends z value be mentioned in both lines 10 and 11* Proposed Change: Also *the D-value* ***and z-value (if appropriate)*** *of the inoculated test pieces/products must be determined….*	
Page 4 Lines 13-		Comment: This sentence as written appears to assume that the BI	

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14		is treated differently than an inoculated carrier described in section 2-1-1. The monograph should allow for either method of recovery. PDA recommends that both sections be worded similarly. Proposed Change: *After exposure to the sterilisation cycle, the custom made biological indicator is* ***enumerated or tested*** *for the presence****/absence*** *of surviving test micro-organisms using a validated, appropriate microbiological technique.*	
Page 4 Line 17		Comment: The full list of information as shown in 2-2 is generally the BI manufacturer's responsibility and not required for the user to maintain. Proposed Change: The following are **the responsibility of the supplier:**	
Page 4 Line 21		Comment: For clarity, revise as shown. Proposed Change: viable spore count expressed to 1 decimal place…	
Page 4 Lines 29-31		Comment: PDA recommends the confidence level be removed because the 95% confidence interval appears to have been taken out of context from the Klaus Haberer paper. Haberer stated that using 1 exposure time in the Stumbo et. al., procedure, with a defined # of replica (for a result within confidence interval of 95% the ISO standard requires at least 50 units). In general manufacturers express values to 1 decimal place. PDA recommends reference to one of the methods in ISO 11138. Proposed Change: … the D-value should be stated in time units and expressed to 1 decimal place.	*A*

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Page 5 Section *3-1-1 Z Value*		Comment: It is not clear if this is a requirement for the user to calculate a z-value or this is specific to the vendor. CoAs do not generally state the D-values used to calculate the z-value. The user would not know if the process temperature is in the range of the 3 temperatures at which the D-values were determined. The implication is also that if the process temperature falls outside of the D-value temperature range a new Z-value must be determined. The 110°C to 130°C is the standard range at which physical lethality is gathered per ISO 11138-3 2006. Proposed Change: It would be more appropriate to move this information on z values to EP General Chapter 5.1.5. *Application of the F_0 concept to Steam Sterilisation of Aqueous Preparations* since the concepts are already discussed there.	
Page 5, Line 22 – Page 6, Line 16		Comment: PDA proposes deleting the information on establishment of the validation cycle as beyond the scope of the chapter. The referenced information (Haberer paper *Section 5*) appears to apply only to steam sterilisation. For example, because of the heat up lag in liquid load products, the approach described is not valid for these types of products. Please see other references such as PDA TR1*Validation of Moist Heat Sterilization Processes: Cycle Design, Development, Qualification and Ongoing Control* or TR3 *Validation of Dry Heat Processes Used for Depyrogenation and Sterilization*. Proposed Change: Delete section 3-1-2 Establishment of validation cycle.	
Page 6 Line 35		*As stated in general chapter 5.1.1, the reference conditions are 160 °C for not less than 2 h.*	

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		Comment: Revise as shown to allow for other time / temperature combinations per General Chapter 5.1.1. Methods of Preparation of Sterile Product. Proposed change: **Other combinations of time and temperature may be used provided that it has been satisfactorily demonstrated that the process chosen delivers an adequate and reproducible lethality when operated routinely within the established tolerances.**	
Page 6: Line 41-42, and 46-47,		Comment: For clarity and in line with the previous comment, PDA recommends revising as follows. Proposed Change: F_H is the equivalent time in minutes at a temperature of ~~170~~ 160 °C delivered by the sterilisation process to the product in its final container.	
Page 7 Line 4		Comment: Revise to allow for other time / temperature combinations (see earlier comment) Proposed Change: *Spores of Bacillus… between 160 and 180°C.* **Other combinations of time and temperature may be used provided that it has been satisfactorily demonstrated that the process chosen delivers an adequate and reproducible level of lethality when operated routinely within the established tolerances.**	
Line 10-12, Page 7		Comment*: PDA proposes deleting* formaldehyde to discourage its use because of its toxicity and oncogenicity. Proposed Change: *A number of gas sterilisation processes are*	

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		currently used, including ethylene oxide, hydrogen peroxide and peracetic acid or combinations of the latter.	
Line 19-20, Page 7		Comment: Change as shown for compatibility with ISO 11135. Proposed Change: *The number of viable spores* ***is greater than or equal to*** *10^6 per carrier.*	
Page 7 Lines 21-25:		Comment: PDA proposes deleting this paragraph since without the appropriate formulas and descriptions, the application to this document is not clear. Proposed Change: Delete the paragraph.	
Page 7 Line 31-47		Comment: The paragraph, *Biological Indicators For Ionising Radiation Sterilisation*, may confuse users. PDA believes the use of dosimeters alone in routine production is scientifically sound and this approach is supported by the ISO 11137 series requirements for qualification monitoring/control of radiation sterilisation processes. Dosimetric release is scientifically valid and widely accepted. Proposed Change: Recommend deleting this paragraph and using the ISO reference.	
Page 7 line 31:		Comment: PDA is not familiar with a scientific reference supporting the use of a spore BI (Bacillus pumilus) in special situations due to "potential for spore protection." Spores or naturally occurring bioburden would both be protected so there is no benefit with the use of spores, as inactivation is dependent on the resistance of the microbial challenge once the radiation penetrates the package/product. AAMI TIR 37: 2013 is devoted to tissue irradiation. It does not endorse the use of spores to validate the	

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		process. In PDA's experience, there is no BI that is scientifically justified to use with radiation and there is no universal minimum sterilization dose, i.e. 25 kGy, that can be applied across all product lines without scientific justification. There are cases in which 25 kGy may be insufficient to achieve an SAL of 10^{-6} Proposed Change: Delete section 5 Biological Indicators for Ionising Radiation Sterilisation	
Page 8: Line 1-19		*BIOLOGICAL INDICATORS FOR STERILISATION GRADE FILTRATION*. Comment: This is an uncommon term using the concept of a biological indicator for describing the "challenge organism" for filter microbial retentivity testing. *Much of the information in this section is redundant with in EP 5.1.1. Section FILTRATION and any new information should be added there.* Proposed Change: *Delete the section on "Challenge organisms for filtration."*	
Page 8 Lines 20-41; Section 7		Comment: Section 7, *Indicators for Depyrogenation Process* is not relevant to the scope of this chapter. See general comments. Proposed Change: Delete Section 7 and include in a separate monograph specific to dry heat sterilization and depyrogenation.	

Please add more rows if needed.