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December 28, 2018

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Reference: PA/PH/Exp. 1/T (18) 11 ANP1
Revision of EP 5.1.5: Application of F Concepts to Heat Sterilisation

Dear European Pharmacopeia Members:

PDA appreciates the opportunity to respond to the proposed change to section 5.1.5 of the European Pharmacopeia Application of F Concepts to Heat Sterilisation. One overall comment would be to consider further detail provision of important formulas to support the terms in the Definitions section. For ease of usage, the formula or a formal reference should be consistently provided for each term for which a standard formula exists. As an example, this section covers F Concepts, but there is no formula or reference to a formula for the related terms Lethality Rate, F value, or F_0 while there is a formula provided for z value. Additionally, a redundant term has been created: The term F_x is provided for a formula that has been previously established for the term F_{bio} or $F_{Biological}$ ISO17665-1:2006 and PDA Technical Report No. 1 (2007 Revision). The creation of this redundant term will lead to unnecessary confusion on the topic of F Concepts.

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 manufacturing and pharmacopeia publications including members representing our Board of Directors and our Regulatory Affairs and Quality Advisory Board.

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

Sincerely,

Richard Johnson
President, PDA
Cc: Tina Morris, Janie Miller



Reference: PA/PH/Exp. 1/T (18) 11 ANP1

Submission of comments on Revision of EP 5.1.5 ‘Application of F Concepts to Heat Sterilisation’

Comments from:

Name of organisation or individual

1. General comments

General comment (if any); The content of the document is inconsistent in the provision of important formulas to support the terms in the Definitions section. For ease of usage, the formula or a formal reference should be consistently provided for each term for which a recognized formula exists. As an example, this section covers F Concepts, but there is no formula or reference to a formula for the related terms Lethality Rate, F value, or F_0 while there is a formula provided for z value. Additionally, a redundant term has been created: The term F_x is provided for a formula that has been previously established for the term F_{bio} or $F_{\text{Biological}}$ ISO17665-1:2006 and PDA Technical Report No. 1 (2007 Revision). The creation of this redundant term will lead to unnecessary confusion on the topic of F Concepts.

Specific comments on text (Reference: PA/PH/Exp. 1/T (18) 11 ANP1):

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
Page 1, 25-26	<p>Comment: For ease of use, add the formula provided for z value immediately below definition. Alternatively, a reference to this term should be provided.</p> <p>Proposed change (if any): The z value can be calculated using the following formula:</p> $z = (T_2 - T_1) / (\log_{10}D_1 - \log_{10}D_2)$ <p>Where: D_1 = D-value of the micro-organism at temperature T_1 D_2 = D-value of the micro-organism at temperature T_2 N_0 = initial number of viable micro-organisms N = final number of viable micro-organisms T = temperature</p>
Page 1, 25-26	<p>Minor comment: There is no mention that the change in temperature of z is usually in deg C, since the D value and F value usually relate to deg C. Minor consideration to add oC <i>“The z-value is the change in temperature (oC) required to alter the D-value by a factor of 10 (the z-value relates the heat resistance of a micro-organism to changes in temperature.”</i></p>
Page 1, 27-30	<p>Comment: The creation of the new term Fx is confusing as it is redundant with pre-existing thermal sterilization terminology terms (e.g., currently recognized in ISO17665:2006 and PDA Technical Report No. 1 (2007 Revision). To minimize confusion, existing and recognized terms should be utilized in this document. The terms, definitions and/or formulas listed below were taken/adapted from ISO11139:2018 and PDA Technical Report No. 1 (2007 Revision).</p> <p>Proposed change (if any): “The lethal rate (L) is a measure of inactivation per unit time at temperature, T, expressed in terms of a reference temperature, T_{ref}”</p> <p>Note 1 to entry: L is expressed as minutes at the reference temperature, T_{ref}, per minute at T.</p> <p>Note 2 to entry: Lethal rate at any temperature can be calculated using the formula:</p> $L = 10^{(T - T_{ref})/z}$ <p>Where :</p> <p>T is the delivered temperature;</p> <p>T_{ref} is the reference temperature;</p> <p>z is the change in temperature that produces a tenfold change in D value.”ⁱ</p> <p>“F value is the measure of microbiological lethality delivered by a heat process expressed in terms of the equivalent time, in minutes, at a specified temperature with reference to microorganisms with a specified z</p>

Line number(s) of the relevant text	Comment and rationale; proposed changes <i>(If changes to the wording are suggested, they should be highlighted using 'track changes')</i>
	<p>value”ⁱⁱ</p> <p>“F_0 value is a measure of microbiological lethality delivered by a moist heat sterilization process expressed in terms of the equivalent time, in minutes, at a temperature of 121,1 °C with reference to microorganisms with a z value of 10 K”ⁱⁱ</p> <p>“F_{BIO} value is a term used to describe the delivered lethality in terms of actual kill of microorganisms on or in a BI Challenge System.”ⁱ</p> <p>The F_{BIO} can be calculated using the following formula: “$F_{BIO} = D_T \times (\log_{10}N_0 - \log_{10}N)$”</p> <p>Where: D_T = D-value of the micro-organism at temperature T N_0 = initial number of viable micro-organisms N = final number of viable micro-organisms T = temperature”^{i, ii}</p> <p>“F_H value is a measure of microbiological lethality delivered by a dry heat sterilization process expressed in terms of the equivalent time, in minutes, at a temperature of 160 °C with reference to microorganisms with a z value of 20 K”ⁱⁱ</p> <p>Thus, a new term F_x, with subscript “x”, will be confusing to those who use F_{BIO} and F_H, (even those using F_0), which make common distinctions of lethality of BI challenges, dry heat sterilisation, and moist heat sterilisation.</p>
Page 2, Line 3 Table Header	<p>Comment: Eliminate use of redundant term F_xvalue.</p> <p>Proposed change (if any): “ F_x value” To: “F value”</p>
Page 2, 4-5	<p>Comment: In reference to the limitation of minimum sterilization temperature of 110C for moist heat and 140C for dry heat; the minimum temperatures of 110 C and 140 C are the minimum <u>acceptable</u> temperatures that can be used for the F value calculations and respective sterilisation processes.</p> <p>Proposed change (if any): The headings in Table 5.1.5-1 should state “Minimum Acceptable Temperatures”</p>
Page 2,	<p>Comment: Eliminate use of redundant term F_xvalue.</p> <p>Proposed change (if any): From: “For both dry and moist heat sterilisation cycles, the relevant F_x value is used to demonstrate that...” To: “For both dry and moist heat sterilisation cycles, the relevant F value is used to demonstrate that...”</p>
Page 1 (lines 27-32) and Page 2 (line 7-8)	<p>Use of F_x value is misleading since it is not defined or mentioned in the EMA Guideline of April 2016 of “)Guideline on the Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container” (EMA/CHMP/CVMP/QWP/BWP/850374/2015)Applying the F_x Concept to Dry heat sterilisation is misleading since it does not mention the use of Biological Indicators. The importance of BIs is stated in the above Guideline but not in the proposed 5.1.5.</p>

ⁱ PDA Technical Report No. 1 (2007 Revision), Validation of Moist Heat Sterilization Processes: Design, Development, Qualification and Ongoing Control.

ⁱⁱ ISO11139:2018, Sterilization of healthcare products – Vocabulary – Terms used in sterilization related equipment and process standards.