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A Review of the Newly Revised ISO 11138 Series on the Manufacture of Biological Indicators

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Mesa Labs manufactures its biological indicators in accordance with several standards. The last edition of Spore News detailed the recent changes to the United States Pharmacopeia regarding biological indicators. This edition discusses changes to the newly revised AAMI/ANSI/ISO 11138 series which details the requirements for the production/performance of biologicial indicators used for the sterilization of healthcare products. The revision to this series was published in February 2017 and most changes to the documents consisted of minor rewording and reformatting. A few changes of note were made regarding ethylene oxide and dry heat D-values which can be found in sections II and IV below.

I. ISO 11138-1:2017 Sterilization of health care products—Biological Indicators, Part 1 General Requirements

A. Section 3—Terms and definitions

Definition of "Inactivation curve" was removed and "Survivor Curve" was added.
Definition of "Packaging system" was removed.
Definition of "Fbio" was removed. Additionally, the use of the term was removed throughout the 11138 series. BI manufacturers historically have not reported this value, but it can easily be determined by the user if desired as the values used in the calculation (population and D-value) are presented on the Certificate of Analysis. (For more info on Fbio, refer to Spore News Vol.4, No. 3)

B. Section 4—General Manufacturing Requirements

In Section 4.2.3 (2006 version) "Test Organism Count" the following sub clause was removed: "If the user requires information on the growth index of the test organism, this shall be provided by expressing the viable test organism count as a percentage of the total direct microscopic count."
"Table 1--Information to be provided by the manufacturer" states labeling requirements. The statement "The name or abbreviation of the culture collection from which the test organism has been obtained and the reference number of the strain", has been removed from the table, however the requirement still stands that the "originating inoculum" be tracable to "a recognized culture collection" (section 4.2.2.1).

C. Section 5—Specific Manufacturing Requirements

No significant changes

D. Section 6—Determination of Population and Resistance

Section 6.1.2 was changed to add a specific reference to ISO 14937 (Sterilization of health care products – General requirements for characterization of a sterilizing agent and the development, validation and routine control of a sterilization process for medical devices) and now reads "Resistance characteristic of biological indicators intended for sterilization processes not specified in any subsequent part of ISO 11138 shall be defined using the specific critical variables of that sterilization process (see ISO 14937)."
Section 6.3.2 has been expanded to provide clarification for subsequent population testing of BIs. This section now states: "Population verification shall be achieved when results fall within 50% to 300 % of the manufacturer's stated nominal population. Confirmation test results of the population determined by end users or manufacturers during stated shelf life may meet the 50% to 300% range, but could fall below the minimum population specification as defined in this document. In these cases, the original population is

considered to be verified if the confirmation test results are within the 50 % to 300 % range." (Emphasis added to newly clarified section). The change makes clear that the user should not consider the results of their internal assay as a re-certification of the manufacturer's label claims.
Section 6.4.3. has been expanded to provide clarification for subsequent resistance testing of BIs. This section now states: "The D-values shall be within +/-20 % of the manufacturer's stated value when determined by the manufacturer during the stated shelf life using the methods specified by the manufacturer. …*Confirmation test results of the D-value determined by end users or manufacturers during stated shelf life may meeting the +/- 20 % requirement but could fall below the minimum D value specification as defined in this document. In these cases, the original D value is considered to be verified if the confirmation test results are within the +/- 20 % range.*" (Emphasis added to newly clarified section). The change makes clear that the user should not consider the results of their internal assay as a re-certification of the manufacturer's label claims.

E. Section 7—Culture Conditions

Section 7.4 is new and relates to software validation for incubators that contain detection systems.
Section 7.5 is new and states: "If a specific detection system is to be used with a specific biological indicator then the combination of the two shall be specified by the manufacturer and used when determining the incubation time."

F. Annexes

a. "Annex A (normative)—Determination of viable count"
No significant changes
b. "Annex B (normative)—Determination of Growth inhibition by carriers and primary packaging materials exposed to sterilization processes"
The test method was unchanged however the number of samples treated to the sterilization process has increased from 12 to 18 carriers. The use of media negative controls has also been added.
c. "Annex C (normative)—D value determination by survivor curve method"
No significant changes
d. "Annex D (normative)—D-value determination by fraction negative method"
No significant changes
e. "Annex E (normative)—Survival-kill response characteristics"
Section E.3.1. has been expanded and states: Not less than 50 replicates shall be used to confirm both the survival time and the kill time… *For lots with a single negative biological indicator in a survival test or a single positive BI in a kill test, an additional 100 samples (minimum) may be tested. If no additional unexpected results are obtained, the survival and kill times are confirmed.*" (Emphasis added to newly clarified section).

II. ISO 11138-2, Sterilization of health care products—Part 2 Biological Indicators for ethylene oxide sterilization processes

A. Sections 3 through 8

No significant changes

B. Section 9—Population and resistance

Section 9.5 adds a clarification that the traditional D-value of "not less than 2.5 minutes" is still a requirement when tested "using test gas mixtures".
Section 9.6 is new and states a D-value of "not less than 2.0 minutes…using a test gas of 100 % EO (see Annex B)." Annex B privides the rationale for these changes in the requirments.

C. Annexes

a. "Annex A (normative)—Method of determination of resistance to ethylene oxide sterilization"
No significant changes.
b. "Annex B (informative)—Rationale for the inclusion of a second minimum D value specification as a result of changes to the test gas used to evaluate resistance and deletion of the requirement for a minimum D value at 30 ºC"
This is a new informative annex.

III. ISO 11138-3, Sterilization of health care products—Biological Indicators Part 3 Biological Indicators for moist heat sterilization processes

A. Sections 3 through 8
No significant changes

B. Section 9
Section 9.5 expands temperature range of D-values which can be used to calculate a z-value from 110°C-130 ºC to 110°C-138 ºC.

C. Annexes
a. "Annex A (normative)—Method of determination of resistance to moist heat sterilization"
The requirement that the resistometer post vacuum be pulled to 10 kPa or less within 1 minute has been changed to 100 kPa in 10 seconds or less.
b. "Annex B (normative)—Calculation of z value coefficient of determination, r2"
No significant changes.

IV. ISO 11138-4, Sterilization of health care products—Biological Indicators Part 4 Biological Indicators for dry heat sterilization processes

A. Sections 3 through 8
No significant changes

B. Section 9
Section 9.5 changes the minimum D-value for 160 ºC from 2.5 minutes to 2.0 minutes.

C. Annexes
c. "Annex A (normative)—Method of determination of resistance to dry heat sterilization"
No significant changes.
d. "Annex B (normative)—Calculation of z value"
No significant changes.

V. ISO 11138-5, Sterilization of health care products—Biological Indicators Part 5 Biological Indicators for low-temperature steam and formaldehyde sterilization processes
No significant changes were made to this part.

VI. Discussion
The 2017 revisions to the ISO 11138 series mainly consisted of minor rewording and reformatting changes. As noted above, the changes of significance were made regarding ethylene oxide and dry heat D-values both of which allow for a lower value. The ethylene oxide value was lowered for the use of 100% gas due to its observed increased lethality as compared to the ethylene oxide blends. The Dry Heat D-value was lowered because commercially produced BIs could not meet the published value.
In conclusion it is important to understand the process under which standards are develped and revised. A statement from the ISO website summarizes this well:

Key principles in standard development
1. ISO standards respond to a need in the market
2. ISO standards are based on global expert opinion
3. ISO standards are developed through a multi-stakeholder process
4. ISO standards are based on a consensus

The ISO 11138 standard series and all standards only remain useful and relevant as long these priniciples are met.

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