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Docket 01D-1093
Dockets Management Branch, (HFA-305)
Division of Management Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

To Whom It May Concern:

The following comments are on the draft guidance document entitled, Premarket Notifications 510K for Biological Indicators Intended to Monitor Sterilizers Used in Health Care Facilities; Draft Guidance for Industry and FDA Reviewers, docket # 01D-0193.

Comment 1 page 19, first full sentence states:

"FDA recommends biological indicators have a minimum Z-value of 10°C; higher Z values may be needed to achieve adequate resistance for biological indicators intended for 132°C and higher temperature cycles."

At the June 18-22, 2001 meetings of the Association for the Advancement of Medical Instrumentation (AAMI), in Washington, DC, the topic of Z values was discussed in a biological indicator meeting, in reference to this document. A representative from the FDA, I am reasonably sure it was Ms. Janie Fuller, was present. After discussion, the group consensus was that a range of Z values should be recommended, rather than setting a minimum of 10°C for a Z value. Z value ranges from 6 to 10°C, or 8 to 10°C were discussed. I do not believe that any specific range was agree to by the group, however, I am reasonably certain that the FDA representative was in favor of stating a range.

Recommendation: State the Z value specification as a range, with a minimum of 6 or 8°C.

Comment 2 same text as above:

I disagree with the statement that higher Z values may be need to achieve adequate resistance for biological indicators used at higher temperatures. The need for an indicator with a higher Z value essentially means that there is a need for a more resistant indicator when testing at higher temperatures. This implies that an indicator that has adequate resistance at 121°C, has the potential to have inadequate resistance at higher temperatures. Using an indicator with inadequate resistance, means, by definition, that there is a risk of releasing non-sterile item because an indicator with inadequate resistance was used. This then implies, that there are organisms (product contaminates) that are more resistant to sterilization at high temperatures than Bacillus stearothermophilus, the usual test organism. I believe the majority of data on steam sterilization would support the claim that an indicator that has adequate resistance at 121°C, will have adequate resistance at higher temperatures in terms of assessing sterilization efficacy. I am unaware of any data that would support the claim that indicators with adequate resistance at 121°C have the potential of being less resistant than potential contaminates at higher temperatures. If this was true, these contaminates would have the potential to still be viable where the indicator organisms have been killed. I am unaware of any literature reports that would support this rationale. Consequently, I disagree that indicators with higher Z values are necessary for high temperature steam sterilization cycles.

Recommendation: Remove the statement indicating a possible need of indicators with a higher Z values for high temperature steam sterilization.

Comment 3 (General):

In our laboratories test experience B. stearothermophilus Z values typically fall within the range of 8 to 10°C. I would consider a Z value of around 8.5 minutes most common, and a Z value of 10°C to be the upper limit.

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Comment 4, page 20 Table 3:

The requirement for a D value of 10 seconds at 132°C is unrealistic as shown below.

A Z value can be calculated with the following formula:

Z value = T_1 - T_2 / log D value T_2 - log D value T_1

Where T_1 is the higher test temperature
Where T_2 is the lower test temperature
Where Log D value T_2 is logarithm of the D value determined at T_2
Where Log D value T_1 is logarithm of the D value determined at T_1

At 121°C, Table 3 requires a minimum population of 10^5, a minimum D value of 1.5 minutes and a Z value of 10°C. An indicator meeting these minimal characteristics, when tested at 132°C, would be expected to have a 7.1 second D value as shown by solving for X in the Z value formula.

10 = 132-121 / log 90 seconds (1.5 min) - log X

Solving for X, X = 7.1 seconds

The specification in table 3 for a minimum D value at 132°C of 10 seconds is higher than the mathematically derived D value of 7.1 seconds.

If the requirement for a D value at 132°C remains set at 10 seconds, then the Z value required, can be calculated as follows:

Z value = 132-121 / log 90 seconds (1.5 minutes) - log 10 seconds

Solving for the Z value, Z = 11.5°C.

B. stearothermophilus rarely has Z value of 11.5°C, therefore, required D value of 10 seconds is very likely unattainable.

Recommendation:

Establish the minimum D value at 132°C, by calculating the D value from the Z value formula, by using the minimum Z value (from the range) and minimum D value at 121°C. If the minimum Z value remains at 10°C, then the minimum Z value at 132°C should be 7.1 seconds. However, if as recommended in comment 1, the minimum Z value is changed to a range, and the minimum of this range is, for example 6°C, then the minimal D value at 132°C would be calculated to be 1.3 seconds. If the lower limit of Z value range is 8°C, then the minimal D value at 132°C calculates to be 3.8 seconds.

Comment 5, page 20 Table 3:

The survival time of 1 minute at 132°C is probably unattainable. Using the formula to calculate survival time, (page 19 mid-page), a survival time of 30 seconds is calculated for a indictor meeting the minimal characteristics at 132°C, i.e., 10^5 and D value 10 seconds. Consequently, the survival time in table 1, 1 minute, is not calculated using the survival formula. In order to attain a survival time of 1 minute, with a 10^5 indicator, the indicator would have to have a 20 second D value. If the indicator had a 20 second D value at 132°C and a 1.5 minute D value at 121°C, it would have a Z value of 16.8°C. Z values of 16.8°C are unheard of for B. stearothermophilus to the best of my knowledge. Even a 10^6 indicator would have to have a D value of 15 seconds in order to have a calculated survival time of 1 minute. If the indicator had a 15 second D value at 132°C, and a 1.5 minute D value at 121°C, it would have a Z value of 14°C. This too is quite likely to be unattainable.

Recommendation:

The survival time should be calculated using the survival formula, the minimally accepted population, and the minimally accepted D value. The minimally acceptable D value should be calculated with the Z value formula, using the minimally acceptable Z value. For example, if the minimum population is 10^5, and the minimum D value at 132°C is 3.8 seconds, the minimum survival time would be 11.4 seconds. The specific minimum time should be derived from calculations and will be variable depending on what is chosen as the minimum population and D value.

Comment 6, page 20 Table 3:

Comments 4 and 5 apply equally as well to the table for steam exposures at 134 or 135°C. In the interest of brevity, recalculations of numbers at 134 or 135°C are not provided. (I could provide this if necessary). As an alternative, below is a suggest revision of table 3.

sterilization cycle	population	D value	Z value	survival time
steam 121°C	10^5	1.5 minutes	8-10°C	5 minutes
steam 132°C	10^5	3.8 seconds	8-10°C	12 seconds
steam 134°C	10^5	2.1 seconds	8-10°C	7 seconds
steam 135°C	10^5	1.6 seconds	8-10°C	5 seconds

This table makes the following assumptions:

- At 121°C a population of 10^5 and D value of 1.5 minutes is acceptable.
- A minimum Z value of 8°C is acceptable.
- D values at 132, 134, and 135°C are determined mathematically, from the Z value formula using 132, 134, or 135°C as T_1, using 121°C as T_2, using 90 seconds (1.5 minutes) as the D value determined at T_2, 8°C as the Z value and solving for the D value at T_1.
- Survival times are calculated using the survival formula, minimal D value calculated from above, and the minimum population of 10^5.

Depending on what is chosen as the lower limit for an acceptable Z value range, the numbers in the table will change accordingly. For example, if the lower Z value is 6°C, the numbers in the table would be recalculated and adjusted accordingly.

Comment 7:

Minimum D values and survival times for 134°C and 135°C should be listed separately. Heat inactivation at high temperatures occurs very rapidly, there are small but significant differences seen between 134 and 135°C.

Summary:

A range of Z values is recommended, perhaps 6 to 10°C, or another range. In my opinion, and in my experience, a Z value of 10°C is towards the upper limit of a Z value for a B. stearothermophilus biological indicator. The D values in Table 3 should be mathematically derived using the Z value formula, and whatever is considered the minimally acceptable Z value (lower limit of the range). The survival times in Table 3 should then be calculated, using the survival time formula, with the mathematically derived D value for that temperature and the minimally acceptable population.

Thank you for the opportunity to comment on this document, and your consideration of the above comments.

Best regards,

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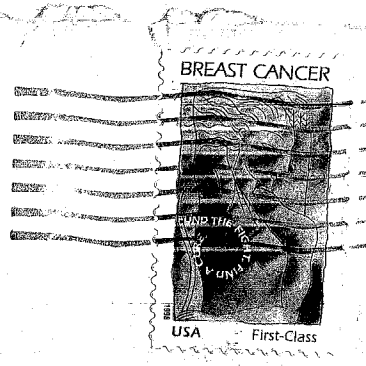

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