3M Health Care

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Dockets Management Branch
Division of Management Systems and Policy
Office of Human Resources and Management Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
(HFA-305)
Rockville, MD 20852

RE: Docket No. 01D-0193

To Whom It May Concern;

The following comments and suggestions are being submitted by 3M Health Care, regarding the document entitled, "Premarket Notifications [510(k)] for Biological Indicators Intended to Monitor Sterilizers Used in Health Care Facilities; Draft Guidance for Industry and FDA Reviewers."

Section I. B. Exclusions

Recommendation:

The following sub-section, 2.A., should be eliminated from the Guidance document:

A. "Enzyme-type chemical indicators…are read separately from (and typically before) the spore growth reading."

Rationale:

This recommendation is supported by a written communication from Tim Ulatowski, Director, FDA/CDRH/ODE/DDIGD, to J. Lewelling, AAMI on June 18, 2001. The communication reconfirms that the "FDA has classified process indicators with both a viable organism component and a spore intrinsic enzyme component as biological indicators based on a high degree of correlation between the two readouts under specified sterilization conditions." A copy of Mr. Ulatowski's communication is included in Appendix A, for reference.

In addition, based on the above rationale, the subject guidance document should also reflect that a spore-associated enzyme component of such biological indicators is most appropriately evaluated using the same test methodology as for the spore itself.

Section I. E. Device Modifications

Recommendation:

The first sentence in the second paragraph should be modified to include the word "may" as follows:

"Some examples of significant modifications to 510(k) cleared biological indicators that *may* require a new 510(k) submission are:"

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Rationale:
This sentence modification is suggested since a decision as to whether or not to file a 510(k), based on a unique set of circumstances, is ultimately left to the judgement of the manufacturer.

Section III. F. Voluntary Standards

Recommendation:
This section should be rewritten to reflect all national and international standards recognized by the agency with an explanation as to why current versions may not be acceptable.
NOTE: All other sections in this guidance document that refer to specific voluntary standards should also be amended to reference only standards that are acceptable to the FDA in their entirety.

Rationale:
The FDA does not, at this time, recognize any current national or international standards for biological indicators. A reference to this modified section should also be included in Section I. F.

Section III. H. Efficacy Data

Recommendation:
The third sentence in the second paragraph should be modified as follows:
"Some biological indicators include two spore species to allow the same product to monitor either steam, ethylene oxide or *dry heat* processes."

Rationale:
Bacillus subtilis spores are used to monitor both ethylene oxide and dry heat processes.

Recommendation:
The second paragraph, last sentence, should be modified as follows:

"Additionally, biological indicators are marketed in test packs (see Section III.J.2), with separate chemical indicators (see Section III.J.3)."

Rationale:
The last portion of the original sentence should be deleted since it refers to a section in the draft guidance document that has been suggested for removal (refer to **Section I. B. Exclusions**, above.)

Section III.H.1 Indicator (Test) Organisms

Recommendation:
The reference to USP, 2000 in the first paragraph should be deleted.

Rationale:
The AAMI standards organization does not recognize the USP standard.

Section III.H.3 Efficacy Studies
Recommendation:
Modify paragraph 1, sentence 3, as follows:
"All studies should test the final finished biological indicator product aged to the end of the claimed shelf-life, consistent with Section III.I. Stability Data"

Rationale:
This reference emphasizes the need for testing of the product throughout the claimed shelf-life.

Section III.H.3.a and b
Recommendation:
Different references for the assay method and D-value determination should be provided.

Rationale:
The standards cited in this section, USP 24 and ANSI/AAMI ST59-1999 Annex A, are not currently recognized by the FDA.

Section III.H.3.b(2) Z-value
Recommendation:
This section, as well as the Z-value column in Table 3, should be deleted from this document.

Rationale:
The requirement for Z-value is inappropriate for biological indicators intended for use in health care facilities. The function of a Z-value is for use in determination of equivalent lethality at different sterilization temperatures. While the Z-value may be appropriate for industrial applications of biological indicators, it serves no purpose for health care facility applications since each sterilization temperature claimed by the biological indicator manufacturer has already been validated with survival/kill values, per section H.3 (Efficacy Studies). The requirement for Z-value determination is therefore not only redundant but could also lead to confusion by the user as this term is unfamiliar in health care facility use of biological indicators.
Additional Comment: If this section should remain in the document, the correct Z-value for steam, per ISO 11138 and EN 866 is a minimum of 6°C.

Section III.H.3.b(3) Survival/Kill window

Recommendation: This section is written to suggest that only the survival time of the BI is critical, and that the kill time may exceed the maximum expected kill time. If this is the case, only the survival time should have to be established.

If the guidance document continues to require the establishment of a kill time, then guidance should be provided as to the extent to which the kill time may be exceeded.

Rationale:
Most current standards require complete survival at the calculated survival time and complete kill at the calculated kill time.

Recommendation:
Modify Table 3 as follows:

Table 3: Minimum Recommended Populations and Resistance Characteristics

Sterilization Cycle	**Viable Spore Population**	**D-Value**	**Survival Time (min)**
Steam 121°C	10^5	1.5 min	4.5
Steam 132°C	10^5	NA*	N/A
Steam 134°C or 135°C	10^5	NA*	N/A
Ethylene Oxide 600mg/L, 60%RH, 54°C	10^6	2.5 min	10.0
Dry Heat 160°C	10^6	3.0 min	12.0

*NOTE: It is not technically possible to generate reproducible D-values between 132°C and 135°C

Rationale:
Changes in the Table 3 are proposed for consistency with above comments.

Section III.H.3.e (2) Incubation Time

Refer to comments for Section XIII. Appendix H (below.)

Section XIII. Appendix H -The Center for Devices and Radiological Health, FDA Guidance for Validation of Biological Indicator Incubation Time

Recommendation:
The following information should be added to the current CDRH Guidance for Validation of Biological Indicator Incubation Time:

"NOTE: The effectiveness of this guideline is described in the following Operating Characteristic Table:

BI Operating Characteristic Table

True Growth Readout	Probability of Acceptance (%)
0.999	0.9903979
0.997	0.9562251
0.995	0.9178823
0.992	0.8321791
0.990	0.7616518
0.983	0.5215836
0.975	0.3001902
0.970	0.1926962
0.963	0.0994861
0.962	0.0910960
0.955	0.0498613
0.952	0.0355577
0.947	0.0221075
0.940	0.0109093
0.938	0.0089218
0.928	0.0028163
0.919	0.0014088
0.913	0.0007643
0.910	0.0005832
0.906	0.0003484
0.900	0.00002263
0.890	0.00000754
0.880	0.00000290
0.870	0.00000117
0.860	0.00000047
0.850	0.00000013
0.840	0.00000005
0.830	0.00000001

This table indicates, for example, that for a theoretical true growth readout of 97%, the probability of biological indicator acceptance is less than 20%. Other statistical approaches for validating reduced incubation time may be considered, such as modifying the RQL and Growth Criteria. However, if alternative methods are utilized, they should be reviewed and agreed to by the agency in advance of the 510(k) submission."

Rationale:

The Biological Indicator Incubation Time Validation Guidance Document as currently written is statistically restrictive. For example, an RQL of 0.037 and growth criteria of 97% are non-discriminating in terms of identifying acceptable versus non-acceptable

product. Based on a statistical simulation, the CDRH Guide was shown to have a probability of acceptance of only 19.3 % for a theoretical true growth readout value of 97%.

Refer to Appendix B-Memorandum H.F. Bushar to J. Fuller, July 8, 1997 (distributed at AAMI Biological Indicator Working Group meeting, June, 1997.)

"Ulatowski, Tim"
<TAU@CDRH.FDA.GOV>

06/18/01 02:18 PM

To:"'jlewelling@aami.org'" <jlewelling@aami.org>
cc: Sue M. Danielson/US-Corporate/3M/US@3M-Corporate
"Lin, Chiu S." <CXL@CDRH.FDA.GOV>
Subject: 3M Attest Products

Joe:

I have attached a statement I crafted in regard to 3M Attest products. There was discussion of them in the AAMI BI WG and I believe there is a need to clarify the FDA position towards them. I expect that 3M will refer to this statement this week. I will follow up this email with a hard copy to you on FDA letterhead.

The Food and Drug Administration evaluates new products under two premarket systems, i.e., premarket notifications and premarket approvals. Premarket notifications (aka 510(k)s) are based on a claim that the new product is substantially equivalent to legally marketed medical devices. In FDA's evaluation we determine whether the data show that the new device is as safe and effective as the predicate devices.

FDA makes every attempt to accomodate new technologies under the 510(k) review process. When a device is found equivalent it assumes the class of the generic type of device or devices to which it is found equivalent. FDA also subcategorizes devices within a generic class of products using so-called product codes.

Devices used to monitor sterilization processes are classified in FDA regulations under the general heading of "steriization process indicators" as either biological indicators or physical/chemical indicators. The regulation defines biological indicators as consisting of a known number of microorganisms that respond to the sterilization process by growth in a suitable media. Physical/chemical indicators are defined as monitoring one or more parameters of the process. They are not organisms but chemical substances.

Indicators that detect changes in bacterial associated enzymes when exposed to a sterilization process to produce fluorescence in a few hours have been marketed. Most enzyme products include viable microorganisms like traditional biological indicators.

FDA has classified enzyme indicator products consisting only of enzymes without viable microorganisms as physical/chemical indicators. FDA has classified process indicators with both a viable microorganism component and spore-intrinsic enzyme component as biological indicators based on the high degree of

correlation between the two readouts under the specified sterilization conditions.

The medical community, including FDA, is sometimes faced with new technology, and we must determine how it fits into practice regimes. We are cognizant of standards relating to sterilization practices. New technology often predates standards and new products should be accomodated until such standards can be reconsidered.

Data submitted by 3M to FDA for the Attest Rapid Readout products show that the fluorescent component of the 3M biological indicators highly correlate to the indicator bacteria response to specified sterilization processes. Labeling for the two component system indicates that the fluorescent readout may be used as the final readout for purposes of release of product. The bacterial growth component may be used to further confirm the findings of the fluorescence component. The labeling indicates that the user determines how and when to use the bacterial readout feature.

In support of the labeling for the Attest Rapid Readout products, it is FDA's opinion that the fluorescent component endpoint alone is suitable for release of product in lieu of the traditional biological indicator endpoint. If the user so chooses, the product should continue to be incubated as labeled and the final color change based on growth documented. Quality control procedures must be followed.

APPENDIX B

FDA Memorandum Regarding Statistical Analysis for AAMI Biological Indicator
(H.F. Bushar to J. Fuller dated July 8, 1997)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
9200 Corporate Boulevard
Rockville MD 20850

July 9, 1997

Lois Jones
Becton Dickenson
P.O. Box 12016
RTP, NC 27709

Dear Ms. Jones:

Subject: Protocol for Validating BI Incubation Time

I have asked the FDA statisticians to conduct an analysis of the proposed protocol for validation of a shortened incubation time for biological indicators (BIs). This was in response to your requested made during the June 9, 1997, AAMI Sterilization Standards Sub-TAG ISO/TC 198/WG 4, Biological Indicators (BI) meeting. Please find the results of that analysis attached.

Based upon these results, I still have all the concerns about incorporating this protocol which I have expressed during the previous working group meeting on June 9, 1997, and October 23, 1996.

However, it is not clear that this issue relates to the above listed documents. I have reviewed the Final 30-Day Review Draft versions of the listed documents, and it appears that references to any method for validating an incubation time have been deleted.

I hope that this information will be useful to you and the working group. Please fell free to contact me if I can be of further assistance.

Sincerely,

Janie Fuller, DDS

Enclosures: July 8, 1997, Bushar message

I N T E R O F F I C E M E M O R A N D U M

Date: 08-Jul-1997 08:40am EDT
From: Bushar, Harry F.
HFB
Dept: OSB_DBS - HFZ-542
Tel No: 827-4361 FAX 443-8559

TO: Fuller, Janie (JYF)

CC: Lin, Chiu S. (CXL)
CC: Campbell, Gregory (GXC)

Subject: Statistical Analysis for AAMI Biological Indicator (BI)

As requested, I have compared statistically the CDRH "Guide for Validation of Biological Indicator Incubation Time" to the 3M "User's guidance on validation of biological indicator incubation time for routine monitoring", which is currently under consideration for adoption by the AAMI Standards Biological Indicator (BI) Working Group. The differences between these two guidelines are as follows: (See page 8 of the 3M presentation.)

Parameters	CDRH Guide	3M Proposal
No. of BI's	>=100 from each of 3 lots	>=200 from each of 3 lots
Effective Sample Size	30-80 BI's per lot	100-194 BI's per lot
Survival Range	30-80%	30-95%
No. of Patial Cycles	>=1 per lot	>=2 per lot
Performance Criteria*	AQL=0.005 at alpha=0.1 RQL=0.037 at beta=0.1	AQL=0.053 at alpha=0.1 RQL=0.094 at beta=0.1
Growth Criteria**	>97% for all 3 lots	>=91% for all 3 lots

*Note these performance criteria differ somewhat from those shown by 3M since 3M assumed only the minimum effective sample size, whereas these criteria are based on simulating the effective sample size by a uniform distribution over the above ranges for the effective sample size.

**Note that 3M erroneously used >=97% for all 3 lots as the CDRH Guide criteria for observed growth at the shortened incubation time.

In order to effectively compare the CDRH Guide to the 3M Proposal, I used SAS to first simulate 1000 effective sample sizes (n) using a random number generator based on the uniform distribution separately for each of 200 assumed true growth readouts (p) from 0.800 to 0.999 by 0.1. Next, the probability of acceptance was then calculated based on the binomial distribution with parameters n and p for each of these 200,000 simulated observations. Finally, the 200 mean probabilites of acceptance were

calculated for each of the 200 p's. This process was performed for each of the two guidelines separately. These results provide the following Operating Characteristic (OC) tables, which completely describe the effectiveness of these two guidelines:

	Probability of Acceptance	
True Growth Readout	CDRH Guide	3M Proposal
0.999	0.9903979	1.0000000
0.997	0.9562251	1.0000000
0.995	0.9178823	1.0000000
0.992	0.8321791	1.0000000
0.990	0.7616518	0.9999999
0.983	0.5215836	0.9999910
0.975	0.3001902	0.9997488
0.970	0.1926962	0.9988017
0.963	0.0994861	0.9932743
0.962	0.0910960	0.9916800
0.955	0.0498613	0.9695989
0.952	0.0355577	0.9513667
0.947	0.0221075	0.9073006
0.940	0.0109093	0.8002795
0.938	0.0089218	0.7571132
0.928	0.0028163	0.5238371
0.919	0.0014088	0.3021943
0.913	0.0007643	0.1855561
0.910	0.0005832	0.1404172
0.906	0.0003484	0.0942012
0.900	0.0002263	0.0462653
0.890	0.0000754	0.0126503
0.880	0.0000290	0.0028549
0.870	0.0000117	0.0005543
0.860	0.0000047	0.0000999
0.850	0.0000013	0.0000152
0.840	0.0000005	0.0000023
0.830	0.0000001	0.0000003

The above table clearly indicates that the 3M proposal would provide consistently higher probability of acceptance for a shortened incubation time than the CDRH guide. Therefore, at relatively high true growth readout, e.g., >0.97, the 3M proposal may be more likely to allow the user to make acceptable decisions to shorten the incubation time than would the CDRH guide. However, at relatively low true growth readout, e.g., <0.91, the 3M proposal may be more likely to allow the user to make unacceptable decisions to shorten the incubation time than would the CDRH guide.

I also checked most of 3M's probability calculations and found the following errors: (Corrected values are underlined.)

*Table on page 6 of the 3M presentation

Probability of Observing Growth Results Less Than Minimum Level of Growth Required

True	No. of	Minimum Level of Growth Required

Growth Readout	Positives at Day 7	91%	95%	97%
91%	30	.51	.77	.94
	80	.43	.86	.98
	100	.41	.90	.98
95%	30	.19	.45	.79
	80	.05	.37	.77
	100	.03	.38	.74
97%	30	.06	.23	.60
	80	.003	.09	.43
	100	<.001	.08	.35
99%	30	.003	.04	.26
	80	<.001	.001	.05
	100	<.001	<.001	.02

*In the Table on page 8 of the 3M presentation, the ISO/WD1461 Annex E AQL=.001 and the RQL=0.030.

In conclusion, the most critical parameter for attempting to shorten the BI incubation time is the required percent of observed growth at the shortened incubation time. Considering that just one surviving BI microorganism would provide sufficient grounds for not accepting the sterilization performed and that these microorganisms have at least been severely stressed by the attempted sterilization, one should require that this allowable percent be 100%! However, since the current requirement for >97% has worked for the last 10 years, one should retain this critical parameter, but not entertain any lower percent of observed growth.

Please contact me for any further statistical analyses.

Thank you very much for your consideration of these comments and suggestions. If you should have any questions regarding this correspondence, please contact me at the address or telephone number provided below.

Sincerely,

Gretchen Keenan, RAC
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