Premarket Notifications [510(k)] for Biological Indicators Intended to Monitor Sterilizers Used in Health Care Facilities; Draft Guidance for Industry and FDA Reviewers

Draft Guidance – Not for Implementation

This guidance document is being distributed for comment purposes only.

Draft released for comment on May 21, 2001

This document will supersede the document "FDA Guide for Validation of Biological Indicator Incubation Time" dated January 1, 1986 once this draft guidance is finalized.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Devices and Radiological Health

Infection Control Devices Branch
Division of Dental, Infection Control and General Hospital Devices
Office of Device Evaluation

Preface

Public Comment

For 90 days following the date of publication in the Federal Register of the notice announcing the availability of this guidance, comments and suggestions regarding this document should be submitted to the Docket No. assigned to that notice, 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.

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Table of Contents

I. Introduction 2

A. Scope 2

B. Exclusions 2

C. Definitions 2

D. Regulatory Authority and Classification of Biological Indicators 5

E. Device Modifications 5

F. The 510(k) Paradigm: Alternate Approaches to Demonstrating Substantial Equivalence 6

II. General Principles Regarding Presentation Of Data 6

A. Editorial Considerations 7

B. Abbreviations 7

C. Data Availability 7

D. Tables and Graphs 7

E. Published Literature 7

F. Protocols and Data Analysis 7

G. Submitting a 510(k) 8

H. Responding to a FDA Request for Additional Information 8

III. Premarket Notification (510(k)) Format and Content 9

A. Cover Letter and Introductory Information 9

B. Table of Contents 10

C. Required Administrative Documentation 10

1. Safe Medical Devices Act of 1990 10
2. Indications for Use Statement 10
3. Truthful and Accurate Statement 10

D. Comparison of the New Biological Indicator to the Predicate 11

E. Description and Specifications of the Biological Indicator 11

F. Voluntary Standards 12

G. Labeling 12

1. Definition 12

2. Content 12

H. Efficacy Data *14*
1. Indicator (Test) Organisms 15
2. Efficacy Study Report 15
3. Efficacy Studies 16

I. Stability Data *21*

J. Accessories *22*
1. Incubators 22
2. Test packs 22
3. Throughput process indicators 23

K. Mail-In protocols *23*

IV. FDA Contacts 24

V. 510(k) Checklist 25

VI. Appendix A - Special 510(k): Device Modification **27**

VII. Appendix B - Abbreviated 510(k) Use of Consensus Standards, Special Controls, and Guidance **29**

VIII. Appendix C – Truthful and Accurate Statement **30**

IX. Appendix D – 510(k) Statement **31**

X. Appendix E – Indications for Use Statement **32**

XI. Appendix F – Declaration of Conformity with Design Controls **33**

XII. Appendix G – Declaration or Certification of Conformity with Consensus Standards **34**

XIII. Appendix H – The Center for Devices and Radiological Health, FDA Guidance for Validation of Biological Indicator IncubationTime **35**

References 39

Premarket Notifications [510(k)] for Biological Indicators Intended to Monitor Sterilizers Used in Health Care Facilities; Draft Guidance for Industry and FDA Reviewers

This document is intended to provide guidance. It represents the Agency's current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind the Food and Drug Administration (FDA) or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

Background

FDA regulates biological indicators intended to monitor sterilizers used in health care facilities as Class II medical devices, requiring premarket notification (510(k)). This draft guidance document recommends the kind of data and information you should submit in a 510(k) for these devices. The use of comprehensive, scientifically sound review criteria help ensure the safety and effectiveness of these devices. FDA recognizes that providing FDA reviewers, 510(k) applicants, and other interested parties information on its review process can promote a consistent and efficient regulatory process. Guidance documents referred to in this document and others that provide information on other medical devices are available on the Internet at the Center for Devices and Radiological Health (CDRH) home page, http://www.fda.gov/cdrh

The effective performance of sterilizers used in health care facilities is important to prevent nosocomial infections. Biological indicators can provide sterilizer users with information on the effectiveness of sterilizer processes. The use of comprehensive, scientifically sound criteria to evaluate biological indicators helps ensure safety and effectiveness of these devices. This guidance document is predicated upon the legal principles of the 510(k) process and draws upon long-standing scientific principles used to evaluate biological indicators. It was produced through interaction with industry, government, academia, and health care professionals.

I. Introduction

A. Scope

This document provides guidance concerning the content and format of 510(k) submissions for biological sterilization process indicators (biological indicator), defined as:

> [A] device intended for use by a health care provider to accompany products being sterilized through a sterilization procedure and to monitor adequacy of sterilization. The device consists of a known number of microorganisms, of a known resistance to the mode of sterilization, in or on a carrier and enclosed in a protective package. Subsequent growth or failure of the microorganisms to grow under suitable conditions indicates the adequacy of sterilization.

21 CFR §880.2800.

FDA encourages sponsors ("you" throughout this document) to contact Infection Control Devices Branch (ICDB) representatives with any questions before submitting a 510(k) for a biological indicator.

B. Exclusions

This document does not provide information on the following biological indicators or related products:

1. Physical/chemical sterilization process indicators, defined in 21 CFR §880.2800(b); chemical indicators are addressed in Appendix I, 510(k) Checklist for Through-Put Indicators.
2. Indicators that do not fit the definition of biological indicator in Section I.A above, such as:
   A. Enzyme-type chemical indicators, also known as rapid readout indicators. Although some enzyme-type chemical indicators are incorporated into devices that also contain a biological indicator, the results of enzyme-type chemical indicators are read separately from (and typically before) the spore growth reading.
   B. Biological indicators intended for use in a manufacturing setting.
   C. Biological indicator organism suspensions or other organism preparations used either as direct inocula for medical devices or to prepare biological indicators.

C. Definitions

Batch or Lot: One or more components or finished devices that consist of a single type, model, class, size, composition, or software version that are manufactured under essentially the same conditions and that are intended to have uniform characteristics and quality within specified limits (FDA, 1996).

BIER/EO gas vessel: Biological Indicator Evaluator Resistometer, a pressure vessel that permits precise control and monitoring of ethylene oxide exposure conditions (ethylene oxide concentration, temperature, relative humidity, and time) with minimal lag times between cycle phases. (AAMI, 1992).

BIER/steam vessel: A Biological Indicator Evaluator Resistometer that uses saturated steam in a pressure vessel and requires minimal time to reach set parameters (AAMI, 1992a).

Biological sterilization process indicator (biological indicator): A device intended for use by a health care provider to accompany products being sterilized through a sterilization procedure and to monitor adequacy of sterilization. The device consists of a known number of microorganisms, of a known resistance to the mode of sterilization, in or on a carrier and enclosed in a protective package. Subsequent growth or failure of the microorganisms to grow under suitable conditions indicates the adequacy of sterilization (21 CFR §880.2800).

Biological indicator: Inoculated carrier contained within its primary pack ready for use and providing a defined resistance to the specified sterilization process (AAMI 1999).

Carrier: Supporting material onto which indicator organisms are deposited (AAMI 1999).

Chemical Indicator (CI): A device intended for use by a health care provider to accompany products being sterilized through a sterilization procedure and to monitor one or more parameters of the sterilization process. The adequacy of the sterilization conditions as measured by the these parameters is indicated by a visible change in the device (21 FCR 880.2800(b)).

D-value (decimal reduction value): Exposure required to secure inactivation of 90% of a population of indicator organisms under stated conditions (AAMI 1999).

Death Rate Curve (or Survivor Curve): The graphic representation of inactivation against increasing exposure to stated conditions (AAMI, 1999).

Inactivation: Loss of the ability of indicator organisms to germinate, outgrow, and/or multiple under specified culture conditions (AAMI, 1999).

Inoculated carrier: Specified material onto which a defined number of test organisms have been deposited (AAMI, 1999).

Kill-time: The exposure time that results in no survival of spores on any carrier.

Lot or Batch: One or more components or finished devices that consist of a single type, model, class, size, composition, or software version that are manufactured under essentially the same conditions and that are intended to have uniform characteristics and quality within specified limits (FDA, 1996).

Medical Device: An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is (1) recognized in the official National Formulary, or the United States Pharmacopeia, or any supplement to them, (2) intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease,

in man or animals, or (3) intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of any of its principal intended purposes (Food Drug & Cosmetic Act §201(h)).

Microbial Sterilization Kinetics: The quantitative mechanisms and effects of physical or chemical sterilization agents on the death of microbes.

Pack, Primary: System that protects the inoculated carrier from damage and contamination without preventing penetration of the sterilizing agent(s) (AAMI, 1999).

Pack, Secondary: Container system in which biological indicators are packed for transport and storage (AAMI, 1999).

Spore (or endospore): The dormant state of an organism, typically a bacterium or fungus which exhibits a lack of biosynthetic activity, reduced respiratory activity, and has resistance to heat, radiation, desiccation and various chemical agents.

Sterilant: An agent that destroys all viable forms of microbial life.

Sterile: State of being free from viable microorganisms (AAMI, 1993).

Sterility Assurance Level (SAL): The probability of survival of microorganisms after a terminal sterilization process, and a predictor of the efficacy of the process (AAMI, 1995).

Sterilization: Validated process used to render a product free of all forms of viable microorganisms (AAMI, 1993).

Survivor Curve: The graphic representation of inactivation against increasing exposure to stated conditions (AAMI, 1999).

Survival/Kill Window: Extent of exposure to a sterilization process under defined conditions when there is a transition from all biological indicators showing growth (survival exposure) to all biological indicators showing no growth (kill exposure) (AAMI, 1999).

Survival time: The exposure time that results in survival of spores on each carrier.

Shelf-life: The maximum length of time a product, in its final manufactured form, should be stored under its labeled storage conditions.

Test Pack: A specific combination of materials and/or containers that have been validated to have a known level of resistance to penetration by a particular sterilant. Biological indicators may be placed in a test pack in order to validate sterilization cycle parameters.

Total kill endpoint analysis: Testing conducted at points below and above the established end point to confirm the germicidal contact time end point.

Validation: Confirmation by examination and provision of objective evidence that the particular requirements for a specific intended use can be consistently fulfilled (FDA, 1996).

Verification: Confirmation by examination and provision of objective evidence that specified requirements have been fulfilled (FDA, 1996).

Viable spore count: Number of viable organisms on an inoculated carrier, estimated by growth of discrete colonies under the labeled culture conditions.

Z-value: For a thermal sterilization process, the change in exposure temperature that corresponds to a 10-fold change in D-value (AAMI, 1999b).

D. Regulatory Authority and Classification of Biological Indicators

FDA regulates medical devices under the authority of the Federal Food, Drug, and Cosmetic Act (the Act). FDA classified medical devices that were in commercial distribution prior to the 1976 Amendments to the Act (preamendments devices) into one of three regulatory classes: Class I, II, or III. The class establishes the regulatory controls that are necessary to provide reasonable assurance of the device safety and effectiveness. Class I devices are subject to general controls. Class II devices are subject to general controls and any FDA-established special controls (as amended by the Safe Medical Devices Act of 1990). Class III devices are subject to premarket approval procedures. You should contact the CDRH Division of Small Manufacturers Assistance (DSMA) for information about general controls (see Section IV. FDA Contacts).

Biological indicators are Class II devices subject to premarket notification (510(k)) requirements (21 CFR §880.2800). FDA has no required performance standards for biological indicators. Biological indicators may be claimed equivalent to: (1) a related classified device that was in interstate commerce before 1976 (preamendments device); or (2) a device cleared through the 510(k) process and currently legally marketed.

Biological indicators intended to monitor sterilizers that use new technology, e.g., microwave or plasma technology, may be claimed equivalent to any legally marketed biological indicator, including a preamendments biological indicator or a biological indicator found equivalent through the 510(k) process.

E. Device Modifications

21 CFR §807.81 states that a premarket notification submission is required when significant modifications are made to a 510(k) cleared device. Persons intending to market a modified 510(k) cleared device should refer to FDA document entitled, "Deciding When to Submit a 510(k) for a Change to an Existing Device, located at www.fda.gov/cdrh/ode/510kmod.pdf and www.fda.gov/cdrh/ode/510kmod.html.

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

1. Change in organism (spore species or strain) used
2. Change in specification for the spore population (or concentration)
3. Change in the primary packaging (or vessel) in which the indicator is maintained prior to and during exposure to the sterilization process

4. Change in the sterilization process parameters (e.g., temperature, time,) or sterilization technology for which the indicator is intended
5. Change in culture conditions and/or processing of the biological indicator subsequent to exposure to the sterilization process, e.g., changes in incubation time, temperature, culture media
6. Change from marketing the indicator separately to marketing the indicator in a test pack
7. Any other modifications to the device that either (a) results in a change in indications for use; or (b) could effect the safety or effectiveness of the device

Note: Under 21 CFR §807.85(b), a distributor who places a device into commercial distribution for the first time under his own name, and a repackager who places his own name on a device and does not change any other labeling or otherwise affect the device, shall be exempt from 510(k) requirements if:

- the device was found substantially equivalent under a premarket notification submission filed by another person; or
- the device was in commercial distribution before May 28, 1976.

F. The 510(k) Paradigm: Alternate Approaches to Demonstrating Substantial Equivalence

Section 510(k) of the FD&C Act requires a person who intends to introduce a device into commercial distribution to submit a premarket notification, or 510(k), to FDA at least 90 days before commercial distribution is to begin. Section 513(i) of the Act stipulates that FDA may issue an order of substantial equivalence only upon making a determination that the device to be introduced into commercial distribution is as safe and effective as a legally marketed device.

The guidance document, "A New 510(k) Paradigm" located at http://www.fda.gov/cdrh/ode/parad510.html describes alternative approaches to the traditional methods to demonstrate substantial equivalence. These alternative approaches are within the existing statutory framework; FDA anticipates they will conserve resources and facilitate the introduction of safe and effective devices into interstate commerce. The alternatives are the Special 510(k) Device Modification, and the Abbreviated 510(k).

The Special 510(k): Device Modification uses aspects of the Quality System Regulation (see VI Appendix A - **Special 510(k): Device Modification**). The Abbreviated 510(k) relies upon special controls and consensus standards (see VII Appendix B - **Abbreviated 510(k) Use of Consensus Standards, Special Controls, and Guidance**).

II. General Principles Regarding Presentation Of Data

A well-written and organized submission facilitates the review process. FDA recommends applicants incorporate the following principles during submission

preparation.

A. Editorial Considerations

FDA recommends applicants carefully edit and review the scientific content of 510(k) documents before submission. We also recommend applicants proofread documents to assure pages are properly numbered (indicated), consecutive, distinctly copied, and readable.

B. Abbreviations

Use of standard abbreviations, such as those acceptable to a peer reviewed scientific journal, help make submissions easier to understand. Also for clarity, documents should define abbreviations in each section, table, and graph where they are used.

C. Data Availability

Retain all data gathered for submissions in a controlled, well-organized, and readily available format for easy access. FDA may request additional information or analysis in order to complete its review.

Bring errors to FDA's attention immediately upon their discovery.

D. Tables and Graphs

When submissions include tables and graphs, FDA recommends the following:

1. Prepare tables and graphs of a quality acceptable to a peer reviewed scientific journal.
2. Identify each table and graph with a title that clearly identifies the nature of the data.
3. Explain all symbols with a footnote or reference page.
4. Provide data tables for interpretation when graphs are presented.

E. Published Literature

When submissions include reprints of or references to published literature or reference methods, to facilitate review, FDA recommends the following:

1. Summarize the information in all referenced published literature.
2. Explain how the information relates to the 510(k) submission.
3. Provide copies or reprints of the published reports.

F. Protocols and Data Analysis

You should provide actual study reports that include all protocols (i.e., describe objectives, materials and equipment, experimental methods, controls, etc.), data and

observations, statistical analyses, conclusions, and comments on the test results. This guidance document provides additional information on protocols and data analysis.

Clearly describe analytical methods. Use recognized analytical and statistical methods when possible. For statistical equivalence, please refer to Blackwelder (1982, 1995).

Specify whether the study is in accordance with good laboratory practices (GLP) regulations (21 CFR Part 58) and explain any deviations.

G. Submitting a 510(k)

Establish that the biological indicator is a medical device subject to 510(k) requirements. 21 CFR §880.2800 defines a biological sterilization process indicator as: "a device intended for use by a health care provider to accompany products being sterilized through a sterilization procedure and to monitor adequacy of sterilization. The device consists of a known number of microorganisms, of a known resistance to the mode of sterilization, in or on a carrier and enclosed in a protective package. Subsequent growth or failure of the microorganisms to grow under suitable conditions indicates the adequacy of sterilization." Biological indicators for other uses may be exempt from 510(k) requirements.

To ascertain whether your product is a medical device subject to 510(k) requirements, you should send a written inquiry, including a detailed device description, proposed labeling, and promotional materials to the FDA contact in Section IV below.

Biological indicators for monitoring new technology sterilizers may present unique challenges. You should discuss these devices with FDA before submitting a 510(k) to identify the data and documentation needed for unique devices and for new indications for use. Request information from the FDA contact listed in Section IV below.

You should include the data or information outlined in each element of this guidance document. Alternatively, you may provide alternative data and explain why it is sufficient to address the element, or explain why data are not needed. If FDA finds a 510(k) submission grossly incomplete, FDA will refuse to accept the document, delete it, and notify the applicant in writing. The 510(k) checklist for biological indicators in Section V may help you assess whether your 510(k) is complete.

H. Responding to a FDA Request for Additional Information

Under 21 CFR §807.87(l), you may amend a 510(k) submission with additional information requested by FDA. If additional information is needed to determine substantial equivalence, FDA will notify you by telephone or in writing. Typically, FDA telephones applicants to clarify minor deficiencies. FDA may notify applicants of more significant deficiencies in writing.

Generally, when FDA requests additional information, it places the 510(k) on hold. You are allowed 30 days to respond. Within 30 days of the request date, you may do one of the following:

1. Respond by submitting the requested additional information in writing as directed; the response is added as a supplement to the original 510(k)
2. Withdraw the 510(k) by submitting a written request to the Document Mail Center
3. Not respond and allow FDA to delete the 510(k)
4. Request a limited extension of the 30-day response period by submitting a written request to the Document Mail Center. You should indicate the 510(k) number and the additional time requested. The time period for extensions is not open-ended and will be determined on a case by case basis.

All FDA requests for additional information list an FDA contact. We encourage you to discuss or clarify requests with the FDA contact before responding.

Responses should clearly indicate the 510(k) number, restate the request (or append a copy of the request), and respond completely. FDA expects responses to address each issue identified in the request. FDA does not evaluate incomplete responses; instead, we notify applicants upon receiving incomplete responses and return the 510(k) to hold status. Also, incomplete responses may raise new questions. Therefore, complete responses will help minimize review times.

III. Premarket Notification (510(k)) Format and Content

A. Cover Letter and Introductory Information

Provide a cover letter that includes the following information:

1. a clear statement that the submission is a Premarket Notification [510(k)] Submission
2. the trade name or proprietary name of the device
3. the common, usual, or classification name of the device (e.g., biological indicator)
4. the establishment registration number, if applicable, of the owner or operator submitting the 510(k)
5. FDA product code: FRC (for biological indicator)
6. FDA review panel code: INCB (Infection Control Devices Branch)
7. a classification statement: Class II (for biological indicators)
8. the name and 510(k) number of the legally marketed predicate biological indicator(s) to which substantial equivalence is claimed
9. the name, address, and telephone number for the 510(k) submission official contact(s)

Note: FDA staff will discuss the 510(k) only with individuals identified in the submission as official contacts.

B. Table of Contents

Include a table of contents that identifies the title of each section and its page number.

C. Required Administrative Documentation

1. Safe Medical Devices Act of 1990

The Safe Medical Device Act of 1990 requires that a 510(k) include either:

510(k) summary: a summary of the safety and effectiveness information in the 510(k) upon which an equivalence determination could be based; or

510(k) statement: a statement that safety and effectiveness information will be made available to interested persons upon request (see Section IX Appendix D – **510(k) Statement**).

Applicants must choose only one to submit. FDA will ask applicants who submit both to withdraw one. 21 CFR §807.92 defines 510(k) summary requirements. 21 CFR §807.93 defines 510(k) statement requirements.

2. Indications for Use Statement

Center for Devices and Radiological Health (CDRH) policy requires that a 510(k) submission provide a statement of the device Indications for Use on a separate sheet of paper (Section X Appendix E – Indications for Use Statement provides the format). The Indications for Use Statement is not the directions for use. Instead, it states the device type and specifies its use(s).

A biological indicator Indications for Use Statement should state:

> the device is indicated to monitor whether sterilization conditions are met during a cycle; and
>
> the type of sterilization process (method) and the cycle parameters for which the biological indicator is validated, e.g., 121°C gravity steam sterilization cycles; or 132°C prevacuum steam sterilization cycles, etc.

3. Truthful and Accurate Statement

According to 21 CFR §807.87(k), the submitters of a 510(k) must provide a statement that, to the best of their knowledge, all information is truthful and accurate, and that no material fact has been omitted. The truthful and accurate statement should be signed by a responsible person of the firm required to submit the premarket notification -- NOT a consultant for the 510(k) submitter. See Section VIII Appendix C – Truthful and Accurate Statement.

D. Comparison of the New Biological Indicator to the Predicate

A 510(k) review compares the subject biological indicator to a predicate biological indicator. The applicant must identify a predicate, and compare and contrast the new biological indicator with the predicate. A comparison summary presented in a table format facilitates review. A detailed narrative comparison may accompany the summary. FDA recommends the content and format shown in Table 1.

Table 1

ELEMENT	NEW DEVICE	PREDICATE
Intended Use: • Method of sterilization • Process Parameters		
Labeling		
Organism: Spore Species & Strain		
Accessories (see Section III.J.)		
Viable spore population		
Resistance characteristics: • D-value • Z-value (steam only) • Survival/Kill Window		
Culture Conditions		
Carrier materials		
Packaging : • Primary Pack • Secondary Pack		
Storage Conditions		
Shelf-life		

E. Description and Specifications of the Biological Indicator

FDA asks applicants to provide a detailed device description, including device design and manufacturing specifications as follows:

1. Indicator organism spore species and strain (if the indicator organism selected is not consistent with Table 2, justify the selection using valid science)
2. Resistance characteristics: D-values, survival/kill times, z-values (steam only)

3. Specification for spore population, including the minimum and maximum spore population per strip (or biological indicator unit) allowed for product release
4. The shelf-life claim for the biological indicator
5. A detailed description of steps used to prepare the biological indicator. Include the source of the organism used to generate spores, the method and conditions (including media) of spore propagation and spore storage conditions before application to the biological indicator strip or vessel
6. Manufacturing specifications and characteristics of the spore carrier material and/or vessel
7. A detailed description of the pack and pack materials. Describe all primary (e.g., glassine envelope that contains spore strips during exposure to the sterilization cycle) and secondary packs (e.g., pack that holds a single glassine envelop, and cartons that hold multiple biological indicators during handling and shipment).
8. For self-contained biological indicators, a detailed description of the culture medium including all components and concentrations

F. Voluntary Standards

Identify any voluntary standard(s) that the biological indicator has or will be validated to meet. Only standards recognized by FDA will be accepted in lieu of performance data. FDA maintains an annually updated list of recognized consensus standards at: www.fda.gov/cdrh/modact/recstand.html. For additional information on the use of voluntary standards in 510(k) submissions, see Section I.F The 510(k) Paradigm: Alternate Approaches to Demonstrating Substantial Equivalence and Section VII **Appendix B - Abbreviated 510(k) Use of Consensus Standards, Special Controls, and Guidance**

G. Labeling

1. Definition

Biological indicator labeling includes all primary pack labels, secondary pack labels, package inserts, and promotional materials. Submit all product labeling in the 510(k). You may submit draft rather than final labeling. You should incorporate all labeling changes made during the 510(k) review and submit the final draft labeling before the device is cleared.

2. Content

Consult the labeling regulation, 21 CFR Part 801, before preparing product labeling. The labeling must comply with this labeling regulation. Some voluntary standards require specific labeling information; declaration or certification of conformance to a voluntary standard includes meeting labeling requirements. Before making claims or declarations (or certifications) of conformance to standards, applicants should assure that labeling meets the standard. Additionally, FDA recognizes the value of clear and informative

labeling; therefore, FDA may recommend specific labeling statements to help ensure user success.

FDA asks that you include the following information in biological indicator labeling:

1. Product name
2. Lot/Batch number
3. Indications for Use: State all conditions for use, including the sterilization process, process parameters (sterilizing agent, concentration, temperature, and (for steam) gravity versus dynamic air removal (pre-vacuum), etc.
4. Contraindications: State contraindications, conditions under which the biological indicator should not be used
5. Name and strain of the indicator organism
6. Spore population level(s)
7. Resistance characteristics for each claimed indication for use. Include the method (conditions of testing) used to determine the resistance characteristics.
8. Shelf-life: state the shelf-life and manufacture date or expiration date. State that the product should not be used after the expiration date.
9. Storage conditions: you should describe recommended storage conditions, using temperature and humidity ranges. FDA believes that terms such as "ambient temperature" are not sufficient. You should indicate other conditions that may impact the biological indicator.
10. Directions for use, including:
    A. Detail the preparation and use of the biological indicator including how to place it into loads and/or test packs as validated (see Section III.H.3).
    B. Specify that the biological indicator should be placed in the most difficult to sterilize location within the sterilizer chamber, and refer the user to the sterilizer instruction manual to determine that location for a particular sterilizer.
    C. Describe user quality assurance procedures.
    D. Describe any needed activation techniques (e.g., for self-contained).
    E. Provide detailed instructions for neutralizing the sterilant residuals, if needed.
    F. Detail the recovery method, incubation temperature, method to inoculate the media with the spores, types of incubator which can be used, incubation time, types of media (including brand name if necessary).
    G. Instructions for reading the biological indicator and interpreting the result. Include a reference color to supplement positive and negative readings whenever written descriptions cannot depict the reading. You should indicate the acceptable time to read the biological indicator, and how long

the biological indicator reading is stable, e.g., how long the color change will last.

11. Name and address of manufacturer and/or distributor.
12. Disposal: State the method for disposal, any neutralizers needed, or hazardous wastes resulting from product use. Direct the user to check local and state regulations for hazardous waste disposal procedures.
13. Warnings: Describe any serious adverse reactions and potential safety hazards or use limitations. Include the steps that should be taken in case of contact with any associated hazards.
14. Precautions: Identify any personal protective equipment that should be worn, facilities that should be used, and any other precautions the user should take to safely use the product. Provide information on chemicals, materials, and agents (likely to be present where biological indicators are used) that could affect adversely the biological indicator. Describe factors affecting shelf-life or performance of the biological indicator.
15. Adverse Reactions: Identify possible adverse reactions following exposure to the product.
16. Emergency and additional information: Provide a telephone number for emergencies or for additional information.

H. Efficacy Data

Health care facilities use biological indicators to monitor sterilization processes. As defined in 21 CFR §880.2800, a biological indicator accompanies devices through sterilization processes and monitors sterilization adequacy by its growth or failure to grow. Biological indicators do not indicate that any given sterilizer load or device is rendered sterile. Instead, biological indicators indicate that conditions to inactivate the biological indicator organisms were achieved at the biological indicator location in a particular cycle. When the user places biological indicators in the most difficult to sterilize location in a device load, the biological indicator result provides some assurance that organisms in devices were inactivated. Health care facilities use biological indicators as part of an infection control quality assurance program along with physical and chemical monitoring.

Biological indicators are of two types: paper strip, which require a separate culture medium; and self-contained, which include the culture medium. Some self-contained biological indicators include growth indicators such as pH sensitive dyes. Some biological indicators include two spore species to allow the same product to monitor either steam or ethylene oxide processes. Additionally, biological indicators are marketed in test packs (see Section III.J.2), with separate chemical indicators (see Section III.J.3), or with indicators that allow for rapid interpretation (prior to the visible growth of spores) on the basis of an enzyme or chemical reaction (see Section I.B).

1. Indicator (Test) Organisms

Bacterial spores are used as indicator organisms because they have high resistance to the various sterilization processes. Spore resistance is complex and many aspects are not well understood. Factors involved include: intrinsic (innate) resistance of the spore species and strain, environmental conditions during sporulation, biological indicator preparation, storage, exposure, incubation, and recovery, and biological indicator carrier and packaging materials. The following Bacillus species and strains are accepted for the uses listed in Table 2 (USP, 2000).

Table 2

Sterilizer type:	**Indicator Organism/Spore:**
Steam	Bacillus stearothermophilus (ATCC 7953 or 12980)
Dry Heat	Bacillus subtilis var. niger (ATCC 9372)
Ethylene Oxide	Bacillus subtilis var. niger (ATCC 9372)

For biological indicators intended to monitor sterilization processes other than those listed in Table 2, you should justify the indicator organism using valid science. To do so, you may conduct testing and submit data, or rely on published literature, if an adequate body of knowledge exists.

Because resistance involves many factors other than spore species and strain, you should characterize and validate biological indicators in the final finished form for your specific indications for use (see Section III.H.3 below).

2. Efficacy Study Reports

Efficacy study reports should provide complete details and include data to support product effectiveness claims. Study reports should meet standards for publication in peer-reviewed scientific journals. Reports should include the following information:

1. A clear statement of the study objective(s).
2. Details of all materials, reagents, apparatus, equipment, etc., for example, culture and subculture media, glassware and other apparatus, and incubation devices.
3. Complete details of all methods, procedures, and techniques used; for example, describe the methods used to:
   A. enumerate viable spore populations
   B. determine biological indicator resistance characteristics
   C. assess sterilant neutralizer effectiveness (if neutralization is needed)
   D. validate recovery ability of media used
4. Information demonstrating the reproducibility of each method or referring to an appropriate standard method. When citing a standard method, state any deviations from the method, and explain the reason for and justify all deviations.

5. All relevant process parameters, exposure conditions (temperature, pressure, sterilant concentration, time, etc.).
6. A complete description of all controls: negative, positive, media, carrier material, neutralizer effectiveness, etc.
7. All results, data, and observations.
8. Analysis of results, including graphs, tables, and charts as needed to best illustrate results. Thoroughly analyze the data and include statistical evaluations. FDA recommends designing protocols to provide sufficient samples and replicates to give statistical significance at the 5% level with a statistical power of at least 90%.
9. Summary of study results.
10. Conclusions reached based upon study results.

3. Efficacy Studies

Efficacy studies should be sufficient to demonstrate that the biological indicator performance is substantially equivalent to the predicate biological indicator, and to support all product claims. Biological indicator studies should be designed to evaluate all claims, critical performance characteristics, and to demonstrate product limitations. All studies should test the final finished biological indicator product aged to the end of the claimed shelf-life. Efficacy studies may be combined with the stability studies (see Section III.I) to evaluate performance over the claimed shelf-life.

FDA expects applicants to validate each claim. If a biological indicator claims to monitor multiple sterilization cycles, each cycle should be validated. For example, if a biological indicator claims to monitor 132°C gravity and 135°C prevacuum saturated steam cycles, the study should evaluate efficacy under both 132°C gravity and 135°C prevacuum saturated steam cycle conditions.

FDA recommends biological indicator efficacy studies evaluate at least three different spore lots, prepared using different spore crops.

To characterize a biological indicator, applicants should evaluate both the viable spore population and the resistance characteristics. Minimum recommended values for each are listed in Table 3. FDA believes the critical measure of biological indicator performance is the survival time under the sterilization conditions that the biological indicator is intended to monitor. To achieve the minimum recommended survival time, either the viable spore population or the D-value should be more than the minimum recommended.

FDA recommends these efficacy studies.

a) Viable spore population assay

Include multiple biological indicators from at least three different spore lots, using different spore crops. For information on assay methods, refer to USP 24 and ANSI/AAMI ST59-1999 Annex A.

Provide in the study report all spore count data, to show the count ranges and reproducibility; mean counts alone are not sufficient. See Table 3 for recommended minimum viable spore populations.

b) Resistance characteristics

You should test biological indicators to show their resistance to the sterilization cycle monitored. To provide meaningful data, you should evaluate biological indicator resistance characteristics under well-controlled and constantly monitored sterilization conditions (parameters), delivered with a minimum come-up (pre-conditioning) time. To provide such conditions, FDA recommends using biological indicator evaluator resistometer (BIER) vessels for resistance tests. BIER vessels that meet the requirements of ANSI/AAMI ST44:1992 (AAMI, 1992) or ST 45:1992 (AAMI, 1992a) for testing ethylene oxide and steam biological indicators, respectively. If no BIER vessel exists for the sterilizer being evaluated, gathering meaningful data may be challenging. In such cases, FDA recommends using control sterilizer parameters to the extent possible during tests, and documenting and justifying that tests were adequately controlled. If resistance tests use sterilizers that do not routinely monitor all critical parameters, you may need to add external monitors to document adequate control during resistance tests.

This section outlines tests that FDA has accepted to evaluate the resistance of biological indicators used to monitor traditional sterilization methods, e.g., saturated steam and ethylene oxide. These tests, such as D-values, assume that the sterilization cycle has linear kinetics. Applicants submitting a biological indicator for a new technology sterilization cycle, for which linear kinetics have not be demonstrated, may need to develop other methods to evaluate the resistance of their biological indicator.

For each sterilization cycle that the biological indicator is claimed to monitor, you should provide the following:

(1) D-value

The D-value, or decimal reduction value, is the exposure required to inactivate 90% of a biological indicator population. See Table 3 for minimum recommended D-values.

Several methods exist to determine biological indicator D-values. FDA recommends determining D-values using the survivor curve method by direct enumeration (SC method) (Pflug, 1990 and AAMI, 1999). The SC

method subjects multiple biological indicators to a series of graded exposures, then counts, plots, and analyzes the number of surviving biological indicators after each exposure. The SC method depicts biological indicator resistance over a wide range of exposures, from all surviving through all killed. The logarithm of the number of survivors is plotted against the exposure. The D-value is read from the survivor curve as the negative reciprocal of its slope. Only if the curve is linear, will the D-value represent the biological indicator resistance over the entire range of exposures. As mentioned above, other methods may need to be developed to evaluate biological indicators for cycles with non-linear kinetics.

Methods other than the survivor curve method base their D-value analysis on proportion of non-surviving biological indicators, also referred to as fraction negative or quantal data. For these tests, groups of biological indicators (usually 20) are subjected to different exposures (times) then incubated for growth. These methods assume a linear survivor curve. Therefore, they may provide support for SC method data, but they do not demonstrate linearity.

The following methods may be used to analyze fraction negative data:

Spearman Karber (SK) method calculates the mean exposure time under defined conditions expected to produce sterility ("mean time until sterility") from a set of quantal data. It then uses the exposure time to calculate the D-value assuming a linear curve from the initial spore population. It allows one to estimate "mean time until sterility" variance and to calculate standard deviation and confidence intervals (Pflug, 1990).

Stumbo Murphy Cochran (SMC) method estimates the number of surviving organisms at an exposure time having a quantal result, then calculates a D-value by extrapolating from that number and exposure time to the initial spore population assuming a linear curve. This method is limited because a D-value can be calculated from minimal data (as little as one quantal result); such minimal data may be biased and confidence intervals cannot be calculated. These limitations may be compensated for by using large numbers of quantal data, and by exposing a large number of biological indicators at each time point (Pflug, 1990).

USP <55> Biological Indicators/Microbiological Methods (USP, 2000e) provides a D value determination method which has also been accepted by FDA.

(2) Z-value

The Z-value, used only for (steam/moist heat) sterilization processes, is the number of degrees of temperature (measured in either degrees

Centigrade or Fahrenheit) required for a one logarithm (10-fold) change in the D-value. 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.

To determine the Z-value, conduct a D-value study at several temperatures in the temperature range of interest. Plot the logarithm of the D-values against temperature to construct a thermal resistance curve. The Z-value is the negative slope of the curve. The greater the number of temperatures studied, the more accurate the Z-value result. FDA recommends studies use at least three different temperatures (Pflug, 1990).

(3) Survival/Kill window

You should conduct a study to determine the survival/kill window. The survival/kill window is the range of exposure to a sterilization process under defined conditions when there is a transition from all biological indicators showing growth (survival time) to all biological indicators showing no growth (kill time). USP 24 (USP, 2000) provides an acceptable test method. The minimum expected survival time and maximum expected kill time can be calculated from the following equations[1] (USP, 2000):

$$\text{Survival Time} = \text{Not Less Than D-value} \times (\log_{10} \text{viable spore population} - 2)$$

$$\text{Kill Time} = \text{Not More Than D-value} \times (\log_{10} \text{viable spore population} + 4)$$

To adequately characterize a biological indicator, you should evaluate and submit information on both survival time and kill time; however, FDA recommends using the maximum expected kill times only as a general guide. Currently marketed biological indicators are designed to indicate a gross failure; they survive only the initial portion of the sterilization cycle and are sometimes killed during the come-up time. FDA recommends that biological indicators meet the minimum expected survival time. Biological indicators may exceed the maximum expected kill time.

Table 3 lists the Minimum Recommended Populations and Resistance Characteristics. To date, industry and FDA have emphasized the survival time. FDA has routinely accepted biological indicators based upon the listed survival times. If you select the minimum D-value and the minimum viable spore population in your device design, the expected survival time will be less than recommended. If you select the minimum

[1] These equations should be used only to estimate the expected survival time and kill time (see Table 1 for the minimum recommended survival times).

recommended D-value, FDA recommends selecting a spore population greater than those recommended in Table 3, in order to meet the minimum survival time.

Table 3 Minimum Recommended Populations and Resistance Characteristics

Sterilzation Cycle	Viable Spore Population	D-value	Z-value	Survival Time
Steam 121°C	10^5	1.5 min	10°C	5 min
Steam 132°C	10^5	10 s	10°C	1 min
Steam 134°C or 135°C	10^5	8 s	10°C	40 s
Ethylene Oxide 600 mg/L, 60% RH, 54°C	10^6	3 min	na	15 min
Dry heat 160°C	10^6	3 min	na	12 min

c) Carrier and Pack Materials

Evaluate the effects of all carrier and pack materials upon the resistance characteristics of the biological indicator. For many biological indicators that use recognized acceptable materials, the performance tests outlined above incorporating adequate controls and using final finished product may address these issues. New carrier materials or new uses (e.g., use in new technology sterilizers) for previously cleared materials may require additional testing beyond the performance studies outlined above.

d) Holding Time

Holding time is the length of time that the exposed biological indicator is held before incubation. Evaluate the effect of the labeled holding time upon the resistance characteristics and recovery of the biological indicator.

e) Recovery Protocols

You should evaluate all recovery protocols, including:

(1) Recovery media

Include the effects of the following:

Media additives (e.g., pH indicators, neutralizers, etc.)

Volumes of media (state the manufacturer and brand name of recovery medium used at each stage of the testing)

For self-contained biological indicators, the effect of the sterilization process on the recovery medium

(2) Incubation time

FDA recommends 7 days as the adequate incubation time for biological indicators used to monitor the traditional sterilizer processes listed in Table 2. To validate incubation times of less than 7 days, use Appendix H – The Center for Devices and Radiological Health, FDA Guidance for Validation of Biological Indicator IncubationTime, available also at: http://www.fda.gov/cdrh/ode/283.pdf

(3) Stability (lasting quality) of reading

You should determine the lasting quality of the biological indicator color change or other reading. Submit data to support all claims for stability of the biological indicator reading. Design test protocols to support the labeled directions for reading and interpreting results, and any recommended indicator storage, e.g., archival quality assurance records.

I. Stability Data

FDA asks applicants to validate biological indicator stability over the claimed shelf-life under the labeled storage conditions. Biological indicators may be unstable at elevated temperatures; therefore, FDA believes accelerated stability tests are inappropriate. Stability tests should use only real time aging. You should evaluate biological indicator stability by demonstrating stable populations and efficacy over the claimed shelf-life. For this reason, 510(k) stability studies may be combined with efficacy studies as discussed in Section III.H above. Stability studies should address all general issues outlined in Section III.H. You should also do the following:

1. To evaluate lot-to-lot variability, select product from at least three different lots made from different spore crops.
2. Establish a sampling plan, and justify that the sample size and sample selection method are adequate.
3. Evaluate multiple time points over the claimed shelf life. Sample frequently enough to characterize adequately all product changes and deterioration. An interval of not more than three-months is recommended, especially for the first year. Six-month intervals may be adequate for the second year, depending upon the shelf-life claim and existing stability data. Sample more frequently if little information is available to support product stability.
4. Provide the following detailed information about the sampling plan and test protocols:
   A. references to any standards, guidelines, used as a basis for stability testing
   B. the size of each lot
   C. the number of samples selected per lot

D. the method used for selecting the samples

E. the time points for analysis

F. the dates of sampling

G. analyses performed

H. the duration of the study

5. State the storage conditions used for the study. Use the labeled storage conditions for the biological indicator; alternatively, use other more deleterious conditions and justify that the conditions are more deleterious.

6. Provide the product's lot/batch or other identification number, and the manufacturing date and age of each lot during the study period.

In lieu of complete stability data supporting the proposed claims, FDA accepts a detailed protocol and sampling plan for ongoing stability studies to be continued after clearance (see description above). Keep all stability data on file in accordance with the Quality System Regulation, (QSR) 21 CFR Part 820.

J. Accessories

1. Incubators

Biological indicator labeling may recommend a suitable incubator. Alternatively, labeling may recommend incubation conditions and allow users to select an appropriate incubator. FDA considers incubators without specific claims to be general use devices, which are exempt from 510(k) requirements. A 510(k) may be required for incubators with additional claims or special features, such as fluorescent readers, etc.

However, incubator performance is an important aspect in biological indicator validation. Some (typically self-contained) biological indicators are marketed as part of a system that includes an incubator. A 510(k) for this kind of biological indicator should include a certification that any incubator sold as part of a system maintains the operating temperature specifications under all potential loading conditions over the recommended incubation time.

2. Test packs

Biological indicator test packs are designed to provide a known consistent resistance to sterilant penetration and to simulate wrapped/packaged goods. Users construct test packs following standard protocols using commonly available items; alternatively, they purchase commercially available test packs. FDA regulates commercially available test packs as accessories to biological indicators. Similar to biological indicators, FDA requires 510(k) clearance of a test pack intended to monitor sterilizers used in health care facilities.

To determine substantial equivalence, FDA compares the new test pack to an already cleared test pack, or to a recognized standard test pack. For example, FDA has cleared steam sterilizer test packs based upon a comparison to the 16-Towel Test Pack described in Annex E of ANSI/AAMI ST46 (AAMI, 1993a). Sterilant penetration resistance is the critical aspect of test pack performance; however, it is not easily measured. Therefore, you may demonstrate test pack performance by analyzing results from biological indicators with known resistance placed inside. You should evaluate test pack performance under all indications for use, including the specific sterilization process type and cycle parameters.

Some biological indicators are marketed as test pack components. To evaluate the effect of the test pack on the biological indicator, the biological indicator's resistance outside the test pack is needed. Therefore, the performance of the biological indicator and the test pack should be validated separately. If the test pack is intended for use with multiple biological indicators, testing should include each biological indicator claimed.

In addition to performance tests, a 510(k) submission for a test pack should contain all elements and items listed in Section III Premarket Notification (510(k)) Format and Content, including a detailed device description, specifications, labeling, etc. Test pack labeling should contain adequate directions for use, including instructions to place the pack in a worst-case load (as indicated in the sterilizer instructions for use) in the "cold-spot" (most difficult location within the sterilization chamber for sterilant penetration). The test pack design should allow for placement in the "cold-spot."

3. Throughput process indicators

Some biological indicator designs include a throughput process indicator. Many process indicators consist of a dye that changes color when exposed to a sterilization process. These indicators help users distinguish processed biological indicators from unprocessed ones. Submissions for biological indicators that include a process indicator should contain complete information about the indicator as outlined in Appendix I Checklist for Throughput Process Indicators.

K. Mail-In protocols

Some manufacturers market biological indicators as part of a monitoring service; the user mails the exposed biological indicator to the manufacturer (or a laboratory) to incubate and read. The handling required by monitoring services may impact adversely upon the biological indicator resistance. Therefore, labeling for biological indicators marketed as part of a monitoring service should detail the handling protocol. The handling protocol should be validated, including the effects of temperature and humidity variations, high altitude ozone, and radiation on biological indicator resistance and recovery.

IV. FDA Contacts

Direct general questions regarding Premarket Notification 510(k) Submissions to:

Division of Small Manufacturers Assistance
Office of Health and Industry Programs
Center for Devices and Radiological Health

Food and Drug Administration

Phone: (800) 638-2041 or (301) 443-6597 or find information at:

http://www.fda.gov/cdrh/dsma/dsmamain.html

Direct questions regarding this guidance document to:

Chief, Infection Control Devices Branch (HFZ-480)
Division of Dental, Infection Control and General Hospital Devices
Office of Device Evaluation
Center for Devices and Radiological Health
Food and Drug Administration
9200 Corporate Blvd.
Rockville, MD 20850

Phone: (301) 443-8913 x143

V. 510(k) Checklist

DATE: **510(k) #:**

Yes	No	N/A	510 (k) ELEMENT (Section to see for details)
			SE Statement or Summary (III.C.1)
			Indications for Use Statement (III.C.2)
			Truthful and Accuracy Statement (III.C.3)
			Comparison of the New Biological Indicator to the Predicate (III.D)
			Description and Specifications of the Biological Indicator (III.E):
			Design
			Spore species
			Spore population / concentration
			Carrier material
			Packaging, primary and secondary
			Culture medium
			Resistance characteristics
			Identify any voluntary standards biological indicator meets or will meet (III.F)
			Provide primary and secondary package labels, and promotional materials
			Labeling provided includes (III.G.2):
			Product name
			Lot/Batch number
			All conditions for use, including sterilization process parameters (sterilizing agent, concentration, temperature, and (for steam) gravity versus dynamic air removal (pre-vacuum), etc.
			Contraindications – conditions under which the biological indicator should not be used
			Name and strain of the indicator organism
			Heat shock spore population / concentration
			Resistance characteristics for each claimed use condition. Include the method (conditions of testing) used to determine the resistance characteristics
			State shelf-life and manufacture date or expiration date. State that the product should not be used after the expiration date
			Storage conditions: using temperature and humidity ranges
			Directions for use (see Section III.G.2 page 13)
			Name and address of manufacturer and/or distributor
			Disposal: method for disposal, any neutralizers needed, or hazardous wastes associated with product use.
			Warnings: adverse reactions and potential safety hazards
			Precautions: personal protective equipment, facilities needed, and other use issues (e.g., chemicals, materials, and agents to be kept away from the biological indicator)
			Provide a telephone number for emergencies or for additional information

			Validate all labeled claims and performance characteristics, including:
			Population assays from at least 3 different spore lots using different spore crops over the claimed shelf-life (III.H.3.a))
			Data supporting claimed resistance characteristics for each claimed use condition over the shelf-life:
			• D-value(III.H.3.b)(1))
			• Z-value (III.H.3.b)(2))
			• Survival/kill time (III.H.3.b)(3))
			Detailed protocols or reference specific standard methods or protocols used to determine the D-values, survival/kill times, and z-values (III.H.2)
			Evaluate effects of carrier material and packaging material upon resistance (III.H.3.c))
			Validate effect of any holding time after exposure to the sterilant, as stated in the labeling, until incubation of the exposed spores upon the recovery of injured spores (III.H.3.d))
			Validate all recovery protocols used in testing and stated in the labeling, including:
			Recovery medium, including additives (e.g., pH indicators, neutralizers, etc.), media volumes, brand name of the recovery medium used at each stage of testing, etc. (III.H.3.e)(1))
			Validate labeled incubation time for recovery of injured spores; if less than 7 days, use CDRH guide (III.H.3.e)(2))
			Evaluate stability (lasting quality) of biological indicator reading (III.H.3.e)(3))
			Validate accessories:
			Incubator (III.J.1)
			Test pack (III.J.2)
			Through-put process indicator (III.J.3)
			Validate mail-in protocols (III.K)

VI. **Appendix A -** Special 510(k): Device Modification

A Special 510(k) is for manufacturers who intend to modify their own currently legally marketed biological indicator. The manufacturer has determined that a new 510(k) is needed for the modification(s) because the modification affects the intended use of the device or the basic fundamental scientific technology of the device. "510(k) A New Paradigm", available at: (http://www.fda.gov/cdrh/ode/parad510.html), contains additional information on when a Special is appropriate.

FDA considers the following modifications to 510(k) cleared biological indicators eligible for Special 510(k) submissions, provided test data demonstrate no decrease in resistance characteristics or stability and no new claims:

1. Change in carrier material
2. Change in primary or secondary pack
3. Change in manufacturing methods (same raw materials) that do not alter the final product specifications that were cleared
4. Change in incubation time

In addition to the basic content requirements of the 510(k) (21 CFR §807.87), you should include the following additional information in a Special 510(k) submission:

1. A coversheet clearly identifying the application as a "Special 510(k): Device Modification"
2. Name of the legally marketed (unmodified) device and the 510(k) number under which it was cleared
3. Items required under Section 807.87 (a)-(f), (h), (j), and (k) including a description of the modified device and a comparison to the cleared device, the intended use of the device, and the proposed labeling for the device (see Appendix D – 510(k) Statement)
4. Declaration of conformity with design controls (see Section XI Appendix F – Declaration of Conformity with Design Controls)
5. Indications for use (see Section X Appendix E – Indications for Use Statement)
6. A summary of design control activities. Include the following:
    a) Identification of the Risk Analysis method(s) used to assess the impact of the modification on the device and its components and the results of the analysis
    b) Based on the Risk Analysis, an identification of the verification and/or validation activities required (including methods or tests used) and documentation that these activities were performed by the designated individual(s) and that the results demonstrate that predetermined acceptance criteria were met
    c) Identification of any manufacturing process controls added/changed as a result of the modifications to the device (e.g., new work instructions, operator

retraining, equipment re-qualification, new inspection aids, additional sampling, etc.)

d) Identification of changes made to the Device Master Record (DMR) related to the modified device – provide document number(s) and revision level(s)

e) Documentation of final design review and sign-off of modified device by designated individual(s)

VII. Appendix B - Abbreviated 510(k) Use of Consensus Standards, Special Controls, and Guidance

Abbreviated 510(k)s are for manufacturers who intend to market a new (not a modified) biological indicator and who rely upon this guidance document as a special control or upon a consensus standard recognized by FDA. The 510(k) paradigm document at: (http://www.fda.gov/cdrh/ode/parad510.html) describes this option in more detail. FDA maintains an annually updated list of recognized consensus standards at: www.fda.gov/cdrh/modact/recstand.html.

You should include the following information in an Abbreviated 510(k):

1. A coversheet clearly identifying the application as an "Abbreviated 510(k)"
2. Items required under Section 807.87 (a)-(h), (j), and (k) including a description of the device, the intended use of the device, and the proposed labeling for the device (see Section VIII Appendix C – **Truthful and Accurate Statement** and Section IX Appendix D – **510(k) Statement**)
3. Summary information that relies on this guidance document; a summary report that describes how the guidance was used to address the risks associated with the device. (If a risk is addressed using an alternative approach, you should include sufficient detail to justify the approach.)
4. A declaration or certification of conformity to the recognized standard in accordance with the following (see Section XII Appendix G – **Declaration or Certification of Conformity with Consensus Standards**):
5. Any element of the standard that was not applicable to the device.
6. State if the standard is part of a family of standards, which includes collateral and/or particular parts, a statement regarding the collateral and/or particular parts that were met.
7. Identify any deviations from the standards that were applied.
8. Identify what differences exist, if any, between the tested device and the device to be marketed and a justification of the test results in these areas of difference.
9. Provide the name and address of any test laboratory or certification body involved and a reference to any accreditation of those organizations.
10. Data/information to address issues not covered by guidance documents, special controls, or recognized standards
11. Indications for Use (see Section X Appendix E – **Indications for Use Statement**)

VIII. **Appendix C –** Truthful and Accurate Statement

[Refer to Section 807.87(k)]

I certify, in my capacity as ***[Title]***, that I believe, to the best of my knowledge, that all data and information submitted in this 510(k) Premarket Notification Submission is truthful and accurate and that no material fact has been omitted.

[Signature]

[Name]
[Title]

[Date]

IX. **Appendix D –** 510(k) Statement

[Refer to Section 807.93]

I certify that, in my capacity as **[*the position held in company by person required to submit the premarket notification, preferably the official correspondent in the firm]***, I will make available all information included in this premarket notification on safety and effectiveness within 30 days of request by any person if the device described in the premarket notification submission is determined to be substantially equivalent. The information I agree to make available will be a duplicate of the premarket notification submission, including any adverse safety and effectiveness information, but excluding all patient identifiers, and trade secret and confidential commercial information, as defined in 21 CFR §20.61.

Certified: *[Signature]*

[Date]

X. **Appendix E –** Indications for Use Statement

Page_____of_____

510(k) Number (if known):

Device Name:

Indications For Use:

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of Device Evaluation (ODE)

XI. **Appendix F –** Declaration of Conformity with Design Controls

Verification Activities:

To the best of my knowledge, the verification activities, as required by the risk analysis, for the modification were performed by the designated individual(s) and the results demonstrated that the predetermined acceptance criteria were met.

[Name]	*[Date]*
[Title]	
[Company]	

Manufacturing Facility:

The manufacturing facility, ***[Company Name]*** is in conformance with the design control requirements as specified in 21 CFR §820.30 and the records are available for review.

[Name]	*[Date]*
[Title]	
[Company]	

[NOTE: The above two statements should be signed by the designated individual(s) responsible for those activities.]

XII. **Appendix G –** Declaration or Certification of Conformity with Consensus Standards

This device is certified to comply with the voluntary standards as contained in ***[identify standard(s) along with edition date(s)]***, as specified and so stipulated above, unless and where specifically so indicated to be at variance with the standard specification, in which case information, data and analysis, or justification for non-applicability, are provided to fully describe the variance and its impact on the device and to justify said variance.

[Name]	*[Date]*
[Title]	
[Company]	

[Note: When there is a third-party certifying laboratory or certification body, provide the names and addresses and a reference to any accreditation of each laboratory. Certification statements should also be included.]

XIII. **Appendix H –** The Center for Devices and Radiological Health, FDA Guidance for Validation of Biological Indicator IncubationTime

Scope:

This guidance applies to all biological indicators, either self-contained or on a strip, which are intended to monitor all types of sterilizers used in health care facilities to sterilize reusable medical devices.

The incubation period for biological indicators may be reduced from the standard seven or more days, provided that, at a minimum, the validation studies demonstrate that the revised number of days of incubation are sufficient according to the following methodology.

Methodology:

FDA allows manufacturers to reduce the incubation time for biological indicators, from the standard seven or more days, if the reduced incubation time is validated adequately. FDA recommends manufacturers validate reduced incubation times using the following methodology.

1. Obtain a minimum of 300 biological indicators. One hundred (100) biological indicators should be from each of 3 separate lots.
2. Using the predefined sterilization parameters, expose the biological indicators in 3 partial sterilization cycles (100 per partial cycle). Each of the test cycles will have 30% to 80% of the indicators surviving (i.e., test positive).
3. A partial cycle is one in which all sterilization parameters, except the time parameter, are met. The exposure time is much shorter than the standard sterilization cycle.
4. Only the biological indicators from one lot are to be used in each partial cycle.Do not mix biological indicators from different lots.
5. It is preferable to run biological indicators in a device load. However, the inherent difficulties of achieving a partial cycle kill under such circumstances are understood. Thus, partial cycles can be run without device loads.

   NOTE: During all sterilization validation studies, consider the effects of the sterilant in combination with the device material on the indicator organism. If the materials are judged to have a significant effect on organism destruction, the biological indicators should be exposed to the sterilant in conjunction with the devices during the partial cycle studies.

6. If there are fewer than 30% survivors or more than 80% survivors in any one run, this particular run is invalid and should be rerun to achieve the desired number of survivors.

7. Three partial cycles are the minimum number of testing cycles to be run. If the results of any one cycle are invalid (see D above), another partial cycle should be substituted for it.
8. After exposure incubate the BIs for a minimum of 7 days. Place the BIs in the growth media no more than 8 hours after removal from the sterilization chamber or removal from the sterilized load of devices. Record the number of positive BIs on either a daily basis or for the particular time interval of interest.
9. Using the number of Bls that test positive on day 7 as the base of 100% grow out (denominator data), determine from the growth chart if the required number of BIs have grown out (numerator data) in the time interval in question. More than 97% of the base number of BIs should test positive in each partial cycle for the proposed incubation time to be acceptable.
10. The greatest number of days of incubation required to obtain more than 97% positive BIs (based on the 7 day incubation time) in any one of the partial cycles is the minimum incubation time that will be allowed. Averaging the three (or more) partial cycle incubation times is not allowable (see example in Appendix).
11. If the biological indicator user has not or cannot validate the biological indicator incubation period using the described methodology, then the user should remain with at least a seven day incubation period.

Number Positive Biological Indicators Required to Achieve 97% Growth

Numerator Data[1]	30	31	32	33	33	34	35	36	37	38	
Denominator Data[2]	30	31	32	33	34	35	36	37	38	39	
Numerator Data	39	40	41	42	43	44	45	46	47	48	
Denominator Data	40	41	42	43	44	45	46	47	48	49	
Numerator Data	49	50	51	52	53	54	55	56	57	58	
Denominator Data	50	51	52	53	54	55	56	57	58	59	
Numerator Data	59	60	61	62	63	64	65	65	66	67	
Denominator Data	60	61	62	63	64	65	66	67	68	69	
Numerator Data	68	69	70	71	72	73	74	75	76	77	78
Denominator Data	70	71	72	73	74	75	76	77	78	79	80

[1] The numerator is the number of positive biological indicators that is greater than 97% of the denominator. If the numerator is equal to or greater than the one listed for the corresponding denominator (based on the total number of positive biological indicators on day 7), the length of the incubation time when this occurs is acceptable.

[2] The denominator is the total number of positive biological indicators on day 7 of incubation.

Example: A manufacturer would like to reduce its biological indicator incubation time to 3 days. The test data show the following:

	Day 1	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Partial cycle #1							
Numerator	0	56	57	57	58	59	59
Denominator	59	59	59	59	59	59	59
Percent Growth	-	94.9	96.6	96.6	98.3	100	100
Partial cycle #2	1	34	35	35	35	35	35
Numerator	35	35	35	35	35	35	35
Denominator	2.9	97.1	100	100	100	100	100
Percent Growth							
Partial cycle #3							
Numerator	0	79	81	Test invalid because percent positive biological indicators is outside the allowable window (30-80%)			
Denominator							
Percent Growth							
Partial cycle #4							
Numerator	0	47	48	49	49	49	49
Denominator	49	49	49	49	49	49	49
Percent Growth	0	95.9	98.0	100	100	100	100

The 3-day reduced incubation time is not validated because, of the three valid partial cycles, not all achieved 97% growth in 3 or fewer days. However, based upon the criteria listed in #5 of the test methodology, the data validate a 5-day reduced incubation time. The 5-day incubation time in this example is the greatest number of days, from all the valid partial cycles, needed to grow out more than 97% of the denominator biological indicators.

XIV. Appendix I Checklist for Through-Put Process Indicators

510(k):

DATE:

REVIEWER:

Is the listed information included in the 510(k) submission?				
Yes	**No**	**N/A**		
			I.	**Device description includes:**
			A.	A description of the chemical reaction that between the chemical indicator and the sterilization process.
			B.	Specifies the conditions under which the chemical indicator will exhibit a color change. If the indicator is labeled to change at more than one temperature, provide data to verify that the indicator will change appropriately at the labeled temperature and not at other temperatures.
			C.	Identifies conditions other than those associated with the sterilization process that can cause the chemical indicator to change. These conditions should be described and cautions listed in the labeling.
			II.	**Labeling does not infer that sterilization has occurred. Labeling includes the following information:**
			A.	Expiration date if applicable
			B.	Storage conditions
			C.	Directions for use
			D.	Exposure conditions
			E.	Parameters measured
			F.	Instructions for interpretation of qualitative or quantitative changes in the indicator
			G.	A color standard, if the indicator undergoes a color change during processing and the user is required to make a subjective decision regarding whether the color change is complete
			H.	Factors affecting shelf-life
			I.	Factors affecting performance
			III.	**Performance testing. The submission provides information to demonstrate:**
			A.	stability of the strip before use (both unopened/shelf-life and opened package/use-life) to validate storage conditions
			B.	the lasting quality (stability) of the color change
			C.	the completeness and uniformity of the color change
			D.	color change is all or none at the conditions measured, unless a color standard is provided on the indicator.
			IV.	**Required Administrative Information**
			A.	510(k) summary of Safety and Effectiveness or a 510(k) Statement
			B.	Indications for Use Statement
			C.	Truthful and Accurate Statement

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