This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

Guidance on
Premarket Notification [510(k)] Submissions
for
Sterilizers
Intended for Use in Health Care Facilities

Infection Control Devices Branch

Division of General and Restorative Devices

March, 1993

Preface

This guidance was developed by the Infection Control Devices Branch, Division of General and Restorative Devices (DGRD), Office of Device Evaluation (ODE), Center for Devices and Radiological Health (CDRH), Food and Drug Administration (FDA).

FDA regulates the introduction of medical devices into interstate commerce. A person intending to market a sterilizer intended for use in a health care facility must submit a premarket notification [510(k)] submission to FDA at least 90 days prior to its introduction into interstate commerce. Regulations governing the general content and format of 510(k) submissions are codified under 21 Code of Federal Regulations, Part 807. These general 510(k) regulatory requirements are further discussed in guidance documents available from the CDRH Division of Small Manufacturers Assistance (DSMA). The intent of this guidance document is to provide additional direction regarding information and data which should be submitted to FDA in a 510(k) submission for a sterilizer intended for use in a health care facility.

Sterilizer technology is expanding at an accelerating pace. Sterilizers can be complex in design and methods of sterilization are diverse. In spite of the complexity and diversity there are some common considerations that can be applied to virtually all 510(k) submissions for sterilizers. FDA believes it is prudent to provide 510(k) applicants, and other interested parties, information describing these common elements in order to improve the quality of submissions and subsequently reduce the regulatory review processing time.

The guidance is based upon current publications, the literature, the combined experience and expertise of agency personnel involved in the evaluation of sterilization processes. Science and the evaluation of medical devices are not static, rather they are evolutionary. As such, FDA may periodically update this guidance, as necessary, to keep it current. Any comments on the content of this document are welcome and should be sent to the address noted under Section R.

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I. Introduction

A. Scope

This document provides guidance concerning 510(k) submissions for sterilizers intended for use in health care facilities, e.g., hospitals, clinics, health care professional offices.

Exclusions

This document does not address the following:

1. sterilizers used in the production or manufacture of medical devices which are regulated under FDA good manufacturing practices regulations (GMPs), 21 CFR Part 820;

2. technologies used only in the manufacturing setting, e.g., ionizing radiation;

3. devices used solely to preclean or otherwise decontaminate medical devices prior to a terminal sterilization process;

4. specific requirements for sterilization wraps, chemical and biological indicators;

5. sterilizers intended for use with contact lenses (separate guidance available from the Division of Ophthalmic Devices/ODE); and

6. sterilizers which employ a liquid chemical sterilizing environment.

B. Definitions

1. Bioburden: The naturally occurring microbial contamination on a medical device prior to exposure to a microbicidal process.

2. Bioburden Based Sterilization: A sterilization process with parameters based upon the predetermined type and concentration of bioburden on the medical devices to be sterilized. This method is used in manufacturing processes and is not appropriate for health care facilities where the bioburden may fluctuate.

3. Biological Indicator (BI): A measured and calibrated number of microorganisms with high resistance to the mode of sterilization being monitored, placed in or on a carrier and packaged to maintain the integrity of the carrier and microorganisms. The microorganism count is known and is higher than the bioburden on the medical device to be sterilized. The BI is used to test the effectiveness of the sterilization process by assessing the microbial lethality of the process.

4. Chemical Indicator (CI): A carrier impregnated or filled with a chemical compound which, when exposed to specific chemical and/or physical conditions, will undergo a known reaction, such as a color change, or produce a measurable quantity of reaction products. A CI indicates that the medical device has been exposed to one or more process conditions, and unless the CI integrates ALL process conditions, it is not an adequate test for assessing the effectiveness of the process.

5. Death Rate Curve (or Survivor Curve): The graphic representation of the microbial sterilization kinetics for a specific microbicidal agent on a defined microbial population.

6. D-value (D_{10}): The time required to kill 90% (one logarithmic cycle) of a homogeneous population of microorganisms. For calculation purposes it is assumed that the killing rate follows first-order kinetics.

7. Inorganic and Organic Load: The naturally occurring or artificially placed inorganic (e.g., metal salts) or organic (e.g., proteins) contaminants on a medical device prior to exposure to a microbicidal process. The naturally occurring organic load is also known as bioburden.

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

9. Overkill Sterilization: A sterilization process that is based upon an arbitrarily established higher initial concentration and resistance of bioburden than that actually expected on the medical devices to be sterilized. Overkill processes typically are based upon a 10^6 colony forming unit (CFU)/unit level of bioburden. This method is to be used for establishing process parameters for sterilizers used in health care facilities.

10. Process and Product Qualification: Elements of the sterilization validation program consisting of selected engineering and microbiological demonstrations performed according to predefined protocols to show process reproducibility and product acceptability.

11. Precleaning: The removal of foreign material, e.g., organic or inorganic contaminants, from medical devices prior to a decontamination, disinfection, or sterilization process.

12. Process Residue: The microbicidal agent or by-products of sterilization remaining on a medical device after completion of the sterilization process.

13. Spore: A dormant state of an organism, typically a bacterium or fungus, which exhibits a lack of biosynthetic activity and reduced respiratory activity.

14. Sterilant: The active agent(s) which achieves sterilization.

15. Sterile: The absolute state where all forms of life have been eliminated. In a practical sense absolute sterility cannot be proven, therefore sterility is considered achieved when organisms are eliminated, inactivated, or destroyed such that they are undetectable in standard media in which they have previously been found to proliferate.

16. Sterility Assurance Level (SAL): A value indicating the probability of a survivor after a sterilization process. For example, an SAL of 10^{-6} is the probability of one in one million nonsterile units after exposure to a sterilization process.

17. Sterilization: An act or process which completely eliminates or destroys all forms of life, particularly microorganisms.

18. Unit: The specified substrate or carrier upon which the specified number of test organisms are inoculated. A unit may be a specified volume, weight, or surface area. For example, a unit could be specified as an entire device, a component of a device (if the device must be disassembled prior to sterilization), or a portion of a device.

19. Vegetative State: An active growth phase of an organism.

20. Validation: A documented program which provides a high degree of assurance that a specific process will consistently produce a medical device that meets its predetermined specifications and quality attributes.

C. Classification of Sterilizers

All medical devices in commercial distribution prior to the 1976 medical device amendments to the Federal Food, Drug, and Cosmetic Act (the act), or so-called pre-amendments devices, were classified by FDA into one of three regulatory classes, Class I, II, or III. The class established the regulatory control to be applied to a device in order to provide reasonable assurance of its safety and effectiveness. Class I devices are subject to general controls as defined in the act (refer to DSMA guidance on general controls). Class II devices are subject to general controls and any performance standards promulgated by FDA. Currently, there are no FDA regulatory standards for sterilizers. Class III devices are subject to premarket approval.

Steam, dry heat and ethylene oxide sterilizers are currently the only sterilizers identified in the classification regulations. They are all Class II devices (see 21 CFR 880.6860, 880.6870, and 880.6880). A new traditional or newer technology steam, dry heat, or ethylene oxide sterilizer may be claimed equivalent to the specific related classified device. Likewise, a sterilizer using a different technology, e.g., microwave, plasma, etc., may also be claimed equivalent to one of the classified devices or to any other legally marketed sterilizer (a pre-amendments sterilizer or one found equivalent through the 510(k) process). Even though a broad range of sterilizer technologies may be eligible for equivalency, FDA is not precluded from finding a sterilizer not substantially equivalent, and thus a Class III device.

D. Related Regulatory Authority

The U.S. Environmental Protection Agency (EPA), under the authority of the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), regulates liquid chemical germicides and other microbicidal agents. A sterilant used in a sterilizer, therefore, may be subject to EPA as well as FDA regulations. Applicants of 510(k)s for sterilizers that use self contained sterilants (e.g., a sterilant in a canister that is connected to a sterilizer) should contact EPA for further direction regarding any applicable EPA regulations.

EPA currently is solely responsible for the regulation of "portable" ethylene oxide sterilizers. This type of sterilizer was intended to include only a bag into which EtO is injected.

Sterilizers (or components thereof) regulated both by EPA and FDA must comply with the requirements of each agency before the sterilizer can be marketed.

II. Documentation

A. Presubmission Considerations for Applicants

1. Establish that the sterilizer is a medical device subject to 510(k) submission, i.e., it is intended for use in a health care facility to sterilize medical products.

2. Discuss new technologies with FDA prior to 510(k) submission to identify any unique aspects of testing or documentation. Contact the Chief, Infection Control Devices Branch as indicated in Part II, Section Q.

3. Determine whether the sterilant must comply with EPA regulations. Prior EPA certification, or concurrent EPA/FDA review is desirable to minimize data redundancy.

4. Ensure that the 510(k) addresses all sections 21 CFR 807.87, Information Required In A Premarket Notification Submission.

5. Ensure that the 510(k) submission addresses all relevant elements of this guidance, or submit a thorough justification for omission of information or data. Use the checklist in Section S.

6. Ensure that there are marketed accessories necessary to achieve a functional system, or concurrent submission of 510(k)s for necessary accessories. For example, acceptable sterilization wraps (except for a flash mode), biological and chemical indicators are necessary to provide a complete system for the user. FDA will not find a sterilizer equivalent until a functional system is in place.

7. Prereview submissions. 510(k)s for sterilizers can be extensive. FDA review of a document is facilitated when the document is arranged in a well-structured format that has undergone a thorough presubmission critique by the applicant to eliminate documentation deficiencies.

B. Recommendations for Protocols and Data Analysis

1. Provide all test protocols which include the objectives, experimental methods, controls, observations, statistical analyses, if possible, or other quantitative analysis, and conclusions and comments.

2. Clearly define the microbial challenge and justify that it is appropriate for the system under examination.

3. Specify the recovery media and ensure that it contains all the elements for abundant growth. Validate the recovery efficiency of the media and submit a summary of the

validation.

4. Define the neutralizer for the sterilant, if needed, and control for its affect upon microbial growth.

5. Ensure that the biological tests evaluate the safety and effectiveness of the sterilizer for the entire specified range of each process parameter.

6. Identify and analyze the factors that will lead to a failure to achieve the required level of effectiveness and reflect these factors in the labeling.

7. Provide tables and graphs to illustrate the results of testing.

8. Provide literature references used for protocols and analyses.

9. Test methods must be scientifically sound and reproducible, and based upon "state-of-the-art" procedures, ideally reflecting a generally recognized consensus of scientific opinion.

C. Documentation for Classified Sterilizers

This guidance identifies the fundamental documentation needed to evaluate the substantial equivalence of a sterilizer. Classified, traditional steam, dry heat, as well as ethylene oxide sterilization processes are well established and much information is available regarding these technologies and their limitations. As such, FDA recognizes that some portions of this guidance are either not critical to the three originally classified traditional sterilizers or the current information base on each type of process is sufficient to satisfy certain data provisions.

Specific sections of the guidance will indicate when the information requested is not needed for a classified, traditional sterilizer. For now, small table top steam or EtO units are not considered traditional for purposes of this document, but FDA may include these devices once industry performance standards are established.

D. EPA Certification

If applicable, provide any registration number assigned by EPA to an EPA regulated sterilant used with the sterilizer, or indicate whether a review by EPA is pending in order to facilitate EPA/FDA interaction on data. Provide a summary of the data submitted to EPA for registration purposes.

E. Reference to Standards, Practices, Technical Reports, Guidelines and Methods

Identify all published standards, practices, technical reports, guidelines, codes, and test methods upon which the design, labeling, and testing of the sterilizer are based. Indicate any deviations from the referenced documents. There are currently no FDA regulatory standards, specifications, or test methods applicable to sterilizers.

The applicant should carefully consider the content of referenced standards, technical reports, guidelines, codes, and test methods in regard to additional design, testing, and documentation provisions not indicated in this guidance. The referenced documents may indicate specifics that are pertinent and unique to the subject sterilizer, whereas this guidance is generalized, i.e., a baseline document. FDA may refer the applicant, if necessary, to additional published documents germane to the subject sterilizer for further guidance. A summary of all tests, conducted in accordance with the referenced documents and in addition to this guidance, should be submitted. The submitter incurs an obligation to abide by any document which the sterilizer is claimed to meet as supportive evidence of safety and effectiveness.

The following documents provide a significant amount of information on validation of new sterilizers, and have been used as references in developing this guidance:

- AAMI Sterilization Standards for steam and EtO
- Block, S.E., Disinfection, Sterilization, and Preservation, Fourth Edition, Lea & Febiger, Phila. Pa. 1991.
- Sterile Medical Devices, A GMP workshop Manual, FDA Publication #84-4174

F. Labeling

The applicant must submit labeling for the sterilizer. Labeling describes the intended use of the device, its operating characteristics, and limitations. These factors are essential in establishing whether the device is equivalent to other legally marketed sterilizers.

1. Device Markings

Indicate the information affixed to the device. Markings may include identifying information, warnings, directions for use, or system requirements. Provide labeling for any accessory sterilants used with the sterilizer, e.g., a chemical agent. Chemical agents regulated by EPA also require mandatory labeling in accordance with EPA regulations.

2. Information Manual

Submit the instructions for use manuals which shall include:

a. the intended use of the sterilizer (listing the medical devices, specific types of materials, and other compatible medical products that can be sterilized by the process);

b. limitations of use (medical devices,types of materials, and medical products that are incompatible);

c. name and address of the manufacturer;

d. type and model designation;

e. installation instructions;

f. detailed operating instructions for all modes;

g. storage and preparation of the sterilant, if applicable;

h. error or fault indications, their cause, and response;

i. interpretation and use of indicator gauges;

j. how to prepare articles for processing including precleaning recommendations and required packaging;

k. post processing information including residue information and sterilant exposure guidance;

l. environmental or other factors affecting efficacy and

safety of the device;

n. any applicable warnings, hazards, and precautions;

o. instructions for routine monitoring including use of chemical, biological indicators, and test packs; and

p. other relevant information regarding the use of the sterilizer and a source of further information should the user have a question.

3. Service Manual [NOT NEEDED FOR TRADITIONAL STERILIZERS]

Submit the service manual for the device which includes:

a. a detailed description of all the tasks that must be accomplished to maintain the sterilizer in proper operating condition, e.g., routine maintenance and inspection instructions, calibration of instruments, etc.;

b. the schedule for these tasks, and;

c. who is responsible for the tasks (user or authorized service personnel).

G. Changes to a Sterilizer Requiring a New 510(k)

The 510(k) regulation states that a new 510(k) is needed whenever the device or the manufacturing process is changed in a manner that may significantly affect its safety and effectiveness. The following are some types of conditions which require submission of a new 510(k) for a sterilizer:

1. A new model number designation unless it is solely a labeling identification change.

2. Any change in sterilization vessel dimensions.

3. A change to software or firmware from a mechanical control.

4. A change in the specific sterilant used in the device. There will be a separate policy available from FDA in April 1993 on changes to certain EtO mixtures.

H. General Description of the Sterilizer

1. Specifications: Design, Construction, Components

a. Provide a complete physical description of the sterilizer. The description can consist of detailed drawings, photographs and brochures. The exterior and

interior dimensions and component locations should be indicated.

b. Describe the materials used to construct the major components of the sterilizer, e.g., the sterilization vessel, jacket, sterilant generator, etc., and certify that the materials meet the sterilizer requirements.

c. Identify all manual or automatic controls, instrumentation, recorders, vents, inputs, outlets, filters, and safety features.

d. Indicate device installation requirements, e.g., electrical, venting, plumbing, etc..

e. Describe the sterilant formulation and its container, if provided as a stand alone accessory to the sterilizer, i.e., sterilant provided in cartridge form, etc.. Provide shelf-life data on the sterilant in its container, including total life if in a multidose container.

f. Describe all accessories marketed with the sterilizer such as racks, trays, carts, etc. Certify that the accessories are compatible with the sterilizer process.

2. Process Parameters

a. Describe all physical and/or chemical process parameters, whether primary to the process or secondary. For example, microwave heat generation may be the primary sterilant but UV irradiation may be generated secondarily. Parameters may include, for example, time, temperature, pressure, humidity, wavelength, intensity, concentration, preprocessing conditions, and postprocessing conditions.

b. Provide the specifications for each parameter.

3. Process Monitors

a. Describe the gauges, chart recorders, displays, etc. which monitor the process parameters. Include information on specifications of the instruments and sensors (accuracy, precision, range, specificity, sensitivity) and relation to recognized standards.

b. Describe the sensor locations within the sterilization vessel. Since sterilizing conditions, e.g., temperature, may vary in different locations in a vessel, indicate how the sensor locations correspond to the relevant "cold spot" in the vessel (least favorable

location for sterilization). Describe how the "cold spot" was determined, e.g., thermocouples. State how all load conditions were considered when determining the dynamics inside the chamber.

c. Certify that the monitors correlate to actual chamber conditions.

d. Describe all fault conditions related to each of the process parameters, including under what conditions a fault is detected and how the sterilizer responds (e.g., indicator, printout, etc.).

3. Software Documentation

Provide the data indicated in the FDA Software Reviewers Guide (available from FDA Division of Small Manufacturers Assistance) for 510(k). Unless otherwise directed by FDA, sterilizers are considered in the 'moderate' risk category described in the software guidance.

I. Cycle Overview

Provide a detailed overview of the sterilization process, in order to provide a foundation for evaluation of the device and test data. Supplement the description by charts, graphs or other visuals detailing all parameters and modes.

J. Test Packs

Test packs are used in validating performance and in routine monitoring of the device once it is commercially available. The test pack is constructed to represent a rigorous challenge to the sterilizer. A biological monitor is placed in the pack and the pack is placed in a worst case load in the cold spot. There should be a test pack for each type of load indicated in labeling. For example, there are fabric, liquid, and wrapped instrument test packs identified for steam sterilizers.

The applicant should refer to relevant standards for test pack specifications, when applicable. Applicants of types of sterilizers with no validated "standard" test pack (e.g., table top units and dry heat) should still devise and validate either test packs for use with their device, or at least test load conditions for purposes of routine monitoring.

Submit a detailed description of the test pack s) used in validating the performance of the device, and that will be used in routine performance monitoring by the user.

Describe the rationale for the composition of the test pack including how the test packs represent a rigorous challenge to the sterilization process. Describe how the test pack itself was validated. Describe the pack and how it is to be used in labeling.

K. Equivalent Devices and Previous Submissions

Identify and compare the subject sterilizer to another legally marketed sterilizer. A finding of equivalence is facilitated the closer the technology of the legally marketed device matches the subject sterilizer. Reference the 510(k) numbers for the claimed predicate devices, if known. Side by side comparisons, whenever possible are desirable (See Attachment 1).

1. Submit labeling for the claimed equivalent sterilizer, if possible.

2. Compare and contrast the technologies.

3. Compare and contrast the specifications.

L. Physical/Chemical Performance Tests

1. Traditional Steam, Dry Heat, and EtO Sterilizers

Certify that the sterilizer will achieve and maintain the relevant physical cycle specifications (time, temperature, sterilant concentration, humidity, pressure, etc.) within specifications under appropriate test load conditions. The required lethal conditions are those determined by biological performance tests (see following sections).

2. Other Sterilizers

a. Describe the rationale for the process parameters and specifications. Briefly summarize how the biological performance test results described in the following sections were used to define the parameters.

b. Provide a summary of physical tests which demonstrate that the sterilizer achieves and maintains the required physical/chemical process lethality conditions within specifications. These data should be from repeated runs with varying load conditions.

H. Biological Performance Tests

1. General

The applicant must unequivocally demonstrate that the device can sterilize, to an acceptable SAL, all the medical products identified in the labeling, when used in accordance with the directions for use.

2. Test Organisms

Since a consistent type and concentration of bioburden cannot be assured or realistically evaluated in a health care facility, an overkill sterilization is necessary. The sterilization cycle is based upon an initial concentration of at least 10^6 CFU (or Plaque Forming Units - PFU)/unit of a highly resistant organism to the process. Typically, the most resistant organism to a sterilization process is used based upon determination of D-values. Table 1 lists the commonly recognized test organisms for the classified sterilizers.

TABLE 1

TEST ORGANISMS FOR CLASSIFIED STERILIZERS

Sterilizer	Organism
steam	Bacillus stearothermophilus (ATCC 7953)
dry heat	Bacillus subtilis var. niger (ATCC 9372 or 19659)
EtO	Bacillus subtilis var. niger (ATCC 9372 or 19659)

The biological lethality profile of a nontraditional sterilization technology must be exhaustively evaluated since the most resistant organism is initially unknown. Table 2 identifies recommended organisms to test for determination of the most resistant organism.

TABLE 2

TEST ORGANISMS FOR NONTRADITIONAL STERILIZERS

A. Bacterial Spores

Bacillus subtilis var. niger (ATCC 9372 or 19659)
Bacillus stearothermophilus (ATCC 7953)
Clostridium sporogenes (ATCC 3584)

B. Mycobacteria

Mycobacterium tuberculosis var. bovis
(or other representative mycobacterium)

C. Nonlipid Viruses

poliovirus Type II

D. Fungi

Trichophyton mentagrophytes (with conidia)

E. Vegetative Bacteria

Staphylococcus aureus
Salmonella choleraesius
Pseudomonas aeruginosa

F. Lipid Viruses

herpes simplex

G. THE LITERATURE OR OTHER INFORMATION MAY SUGGEST ADDITIONAL TEST ORGANISMS DEPENDING UPON THE TECHNOLOGY OR THE TYPICAL BIOBURDEN ENCOUNTERED BY THE ARTICLES INTENDED FOR REPROCESSING IN THE STERILIZER.

3. Biological Test Battery

The biological test data shall include the following:

a. a summary of the sporicidal screening test [NA* FOR TRADITIONAL STERILIZERS];

b. the sterilization process equivalent time (F value) [STEAM AND DRY HEAT ONLY];

c. determination of D-values based upon (1) survivor curve analysis, and (2) fraction negative analysis [NA FOR STEAM AND DRY HEAT or as alternative to item b. above for steam and dry heat);

d. 1/2 cycle Analysis, and Total Kill End Point Analysis [NA FOR TRADITIONAL STERILIZERS except 1/2 Cycle Certification for Traditional Sterilizers];

e. simulated AND in-use tests with representative medical products indicated in labeling [NA FOR TRADITIONAL STERILIZERS except as noted]; and

f. comprehensive analysis of all biological test data and determination of the process parameters.

* NA = Not generally applicable but could be requested if other data or information are equivocal.

Sporicidal Screening Test

The applicant must provide a summary of the American Association of Official Analytical Chemists (AOAC) Sporicidal Test, Section 966.04, Volume 1, Page 141 [Horowitz, William, ed. Sporicidal test - official final action. Official Methods of Analysis of the Association of Official Analytical Chemists. Current Edition. Association of Official Analytical Chemists, Washington, D.C.]. This test is also used for EPA registration purposes. If EPA accepts or requests another test for registration purposes for an EPA regulated sterilant used with the subject device then a summary of the results from that test should be provided. Indicate the specified time for sterilization.

Sterilization Process Equivalent Time

Thermal resistance of microorganisms can be considered in terms of equivalent process times (F_t) at a given temperature. Saturated steam and dry heat sterilizers are special cases where equivalent times are useful for evaluating the acceptability of the process conditions.

Typically, dry heat and gravity steam sterilizers each employ similar operating modes and process conditions as a group (e.g., 121° C and 15 psi for a regular steam cycle). Some dry heat and steam sterilizers may vary from the norm. As a general rule, a higher temperature results in a higher rate of death of microorganisms. Still, there are constraints to saturated steam and dry heat process conditions in order to maintain acceptable lethality conditions.

Physical parameters and microbicidal effectiveness with standard test organisms have been extensively characterized for steam and dry heat sterilizers. Actual operating temperatures can be correlated to a sterilization process equivalent time, or F_o value (a special case equivalent time), at standard temperatures. Saturated steam operating temperature can be converted to equivalent microbial lethality anticipated at 121°C while dry heat temperatures can be converted to 170°C equivalent process times. An F_o of 12 (minutes) for both processes is minimally acceptable (12 log reduction). The method for conversion of process parameters is beyond the scope of this document. Mathematical methods are extensively described in the literature.

Submit the equivalent process time and its method of derivation for the saturated steam or dry heat sterilizer for all modes of operation.

D-Value Determination

The D-value of an organism exposed to a specific sterilization process can be established by one of two methods, survivor curve analysis or fraction negative analysis. For unclassified sterilizers the resistance profile of a battery of test organisms should be determined using survivor curves. Once the most resistant test organism is identified (or possible candidates that require more testing) with preliminary D-values from survivor curves, then tests should be conducted using the fraction negative method. A survivor curve is a necessary precursor to fraction negative analysis to roughly estimate the quantal region (the 10^{2} - 10^{-2} CFU/unit vs time region) for a particular test organism. If different types of loads are provided in labeling (e.g., liquid, fabric, instruments) then the applicant must evaluate the kinetics in each type of load.

The following is a brief overview of methods and data to be reported. For more detail, refer to the literature.

Survivor Curve By Direct Enumeration

A survivor curve plots the surviving microorganisms against a critical process parameter, usually time. The curve provides an important graphic representation of the kinetics of the microbicidal process. The curve should be based upon at least 5 replicated data points using the test organism. Separate curves should be established for "clean" test organisms and for test organisms prepared in an inorganic and organic load of hard water and serum, respectively. The organic load shall be at least 5% bovine serum. The organic load shall be hard water as defined under AOAC test method 960.09 E. (referenced above). Controls must be fully described.

In one variation of a survivor curve determination, a specified concentration of the test organism is prepared on a carrier. The test organism is placed in the sterilizer in a simulated load configuration. The most rigorous load conditions may vary with the sterilizer technology and mode of operation and it is up to the applicant to determine the most rigorous load conditions. The process proceeds for a fraction of the total process time, the test organisms are withdrawn and neutralized, if necessary, extracted from the carrier, if necessary, serially diluted, and placed onto validated growth media. The surviving organisms are directly enumerated. In this method multiple fractional tests are needed to assemble sufficient data to define the survivor curve. The tests are repeated and curves established with different loads to evaluate variability in process kinetics and optimal load configurations. This information defines the process conditions that are noted in labeling. Other test variations may use BIs and BIs in test packs, but the applicant must justify that whatever method was used represents worst case

conditions.

Plot the survivor data on semi-logarithmic paper and calculate a line of best fit, $y = mx + b$ where:

m = slope
x = time
y = log of number of survivors
b = the y intercept at time 0.

Statistically evaluate the data using regression analysis (ANOVA) and submit the analysis. Any adjustment of the curve or analysis, e.g., dropping of points, must be fully justified.

The D-value is the negative reciprocal of the slope of the survivor curve (-1/m). This analysis is valid if the dynamics of microbial kill follow first order kinetics, e.g., data are linear. Linear correlation is evaluated as part of the ANOVA analysis.

Care must be taken not to underestimate a D-value which occurs when (1) there are insufficient replicates (2) the intercept ratio (ratio of the y intercept to the initial inoculum IR = Yo/logNo) of the survivor curve is one or greater, or (3) the death rate curve is inappropriately extrapolated.

An initial test inoculum greater than 10^6 CFU/unit, if possible, is recommended in order to minimize the effect of counting inefficiency below the 10^2 CFU/unit level and to extend the assurance of linearity of lethality beyond a 6 logarithmic range.

Fraction Negative Method

The fraction negative method is another means to derive D-values. In one variation of a fraction negative test, replicate test organisms as described above are exposed to a fraction of the total process time that correlates to the quantal region (10^2 to 10^{-2} CFU/unit vs time region), then the replicates are transferred to validated growth media, and incubated. As above, repeated tests with clean test organisms and those prepared in an inorganic and organic load should be accomplished. Controls must be fully described. The fraction of samples in a test group negative for each time interval are used in deriving the D-value using either (1) the Stumbo-Murphy-Cochran Method, or (2) the Spearman-Karber Method. Again, rigorous load conditions must be considered.

1. Stumbo-Murphy-Cochran Method: The Most Probable Number of organisms at each time point are determined using the Halvorsen-Ziegler equation

$N_u = 2.303 \log (r/q) \times (r)$ where:

r = number of replicates
q = the number of negative replicates
N_u = the number of survivors in r replicates

The D-value is then derived by D = U/Log a - Log b where:

U = the process time
Log a = the initial number of organisms
Log b = Log N_u.

2. Spearman-Karber Method: This method uses a mean time until sterility to calculate a D-value. This calculation is somewhat more rigorous since it permits a valuable statistical evaluation of the derived D-value. The following equation is used

$D_t = U_{sk}/\log N_o + 0.2507$ where:

U_{sk} = Spearman-Karber heating time estimate
N_o = initial inoculum
D_t = D-value

Whenever possible, the Spearman-Karber method should be used and statistical evaluation submitted.

1/2 Cycle Validation, and Total Kill End Point Validation

Once a D-value and preliminary process parameters are established (e.g., to achieve an SAL of 10^{-}), the effectiveness of the process should be further confirmed by a 1/2 cycle Validation and a Total Kill End Point Bracket Validation. The two tests can be combined.

In a 1/2 cycle validation for traditional sterilizers, replicates of the most resistant organism on appropriate carriers (or BIs in test packs) are placed in a simulated worst case condition load at the cold spot and exposed to 1/2 the sterilization process. The test organisms are then incubated in validated media under appropriate conditions along with controls. The media should not exhibit any growth. What constitutes a 1/2 cycle for a nontraditional sterilizer (e.g., a multistep process) should be well defined. It may consist of a ratio of steps, and/or may require several tests of holding one step constant while varying other steps.

For traditional sterilizers, FDA will accept a certification of expected performance for the 1/2 Cycle Test.

In the Total Kill End Point Bracket Validation, a somewhat more rigorous procedure, replicates units with a 10^{6} CFU/unit inoculation of the most resistant test organism (or BIs in test packs) are placed in a test load simulating the worst case condition at the cold spot. A test load is exposed to 1/2 the sterilization process (typically 1/2 the process time) and other test loads at incremental times greater than and less than the calculated 1/2 cycle. At least five increments above and five below the 1/2 cycle time are recommended with at least 110 total test units evaluated (10 per time point including the 1/2 cycle). The time increments should span 1/2 of the total process time (from 1/4 cycle to 3/4 cycle). Alternative methods should be described in detail and justified.

The test organisms are then grown in media that support abundant growth and a representative number from each time point are grown at differing conditions to promote growth of injured organisms. Incubation times should be extended to at least 3-4 weeks to optimize the potential for recovery and growth of viable organisms.

The data should identify no growth at conditions equal to and beyond the 1/2 cycle (i.e., no "skips") and corresponding growth under conditions less than the 1/2 cycle. As always, appropriate controls should be run concurrently. Skips or other failures beyond the 1/2 cycle must be thoroughly evaluated and discussed in the submission. Adjustment of the cycle parameters may be required to ensure sterility.

Other Methods

A total kill validation is also described in literature where replicate runs are evaluated for total kill. This process is less reliable as far as basic cycle validation is concerned, but it conceivably could be appropriate for a particular type of sterilizer technology that is not amenable to traditional forms of analysis. A limited total kill method is used in the final qualification validation as described below in Section Q.

Simulated and In-Use Tests

Simulated or in-use tests are not required for traditional, classified sterilizers except when articles are indicated in the labeling for traditional sterilizers that are not identified in predicate devices, or are not generally recognized in the literature and by the infection control community as usually being sterilized with the particular process. Public health risk concerns may demand that FDA require additional testing from time to time to (re)validate traditional sterilizer effectiveness. For example, additional testing has been requested for dental handpieces.

Sterilizers that are tested in health care facilities are subject to the investigational device exemptions (IDE) regulation, 21 CFR Part 812, if the processed medical product is intended to be returned to service without first undergoing a follow up sterilization procedure with a legally marketed sterilizer.

Simulated Use Tests

Sterilizer microbicidal performance must be tested under simulated use conditions. The applicant must justify how the simulation correlates to in-use worst case conditions.

Select a representative sample of medical products indicated in labeling. The tests must consist of replicates of devices and types of materials that are indicated for sterilization, e.g., metals, polymers, elastomers, adhesive resins, paper, and fabrics. The articles selected for each material should exhibit design configurations that will provide the greatest challenge to penetration of the sterilant, e.g., lumens, mated surfaces, hinges, gnarled surfaces. Test loads should be as noted in labeling, packaged properly, and oriented according to labeling.

The test articles must be inoculated with a 10^6 CFU/unit of the most resistant test organism prepared with an inorganic and organic load. Allow the inoculum to dry on the article before placement in the sterilizer. The inocula must be placed in various locations on the test articles including those least favorable to penetration and contact with the sterilant, e.g., lumens, mated surfaces, hinges. Include controls for each type

of article.

In Use Tests

Sterilizer performance must also be verified under in-use conditions. Articles sampled after use should be precleaned (or decontaminated) according to the normal operational reprocessing protocol of the health care facility where the samples are obtained. Assurance of meeting a stringent precleaning protocol is not a precondition since the robustness of the sterilization process is part of this evaluation. Multiple tests with differing load conditions as indicated in labeling should be reported.

After processing, the test articles are neutralized, if necessary. The articles are immersed in the growth media, if possible, or subjected to an extraction method with the extract placed in growth media. Publications and the literature contain suitable extraction methods.

Derivation of the Process Parameters

The process parameters for the sterilizer shall be derived from the screening test, process equivalent times, D-value calculations, simulated or actual use testing, 1/2 cycle and End Point tests, and any additional safety factors. For process validation an SAL of at least 10^{-6}, based upon the most resistant test organism, shall be demonstrated. Provide a thorough description of the derivation of the process parameters.

N. Toxicity of the Sterilant and Process By-Products

The sterilant and/or the by-products of sterilization may be toxic. The applicant must determine the toxicity profile of the sterilant, and the nature and level of the sterilization by-products and their toxicity profile. Toxicity data for the sterilant and its by-products may be part of a submission for EPA registration. If so, a summary of the data should be submitted in the 510(k).

Selection of the appropriate test protocol and experimental conditions to establish the toxicity of the sterilant(s) and by-products is influenced by several factors, including the potential routes of exposure, the anticipated magnitude of exposure, and physical/chemical properties of constituents of the agent or its by-products. The testing may vary depending upon the antimicrobial agent, its intended use, and directions for use. It is incumbent upon the applicant to select reliable state-of-the-art methodologies to demonstrate the safety of the antimicrobial agent for its intended use. Data submitted to EPA may not address all of the above factors.

Details of the types of tests necessary to derive toxicity data are beyond the scope of this document. The submitter should refer to the Tripartite Biocompatibility Guidance for Medical Devices, the literature, and other relevant publications for more information.

O. Elimination of Toxic Process Residues

The sponsor must establish what sterilant or by-products residues remain on/in the medical product. The concentration of residue may vary depending on the product. The identity of the residue, its concentration on/in the various materials processed (scope of materials defined in labeling), and a comparative analysis of these values to a known toxic level must be determined and presented in the 510(k).

The applicant must describe the means to reduce a toxic level of residue to an acceptable level. Test data must be submitted which demonstrate that the procedure to reduce the residue is effective under all potential conditions. Labeling must include the procedure.

P. Processed Device/Material Qualification

Introduction

Labeling for a sterilizer indicates the types of medical devices and other medical products and/or the component materials of a medical device or product that are compatible with the sterilization process (noted in this section as "articles"). Data shall be provided which attest to the compatibility of each of the listed articles with the sterilization process. The data shall address the effects of the process on the safety and effectiveness, e.g., functionality/specifications, of the claimed compatible articles, and the effects on the biocompatibility of the articles.

The applicant must carefully consider labeling and the implications of the scope of the compatible articles on the potential test regimen. If the articles in the intended use statement in labeling are limited and specifically characterized then the scope of testing is a relatively simple matter. As the intended use becomes more generalized the scope of testing becomes more complex. For example, if ASTM 316 stainless steel instruments are indicated as compatible devices then the test article is basically defined. On the other hand, reference to "metal" instruments connotes a plethora of material possibilities. The same is true regarding a general reference to "polymers" rather than a specific class and type of polymer.

When the labeling indicates a general class of articles that could be differentially affected by the sterilization process, the applicant must specify and justify a representative sample of articles from the class for testing. Even after 510(k) submission the applicant should continue with a vigorous program to analyze new products and those articles that were not tested in the defined class. These data may serve as a basis for labeling revisions or as a resource for users on the compatibility of the sterilizer. As noted in the labeling section, users should be directed to call the manufacturer to obtain any current information on devices and materials not listed in the labeling.

Even though testing may qualify an article for the subject sterilization process the labeling of the article may identify a specific type of sterilization process to be used. In this case, the labeling for the subject sterilizer cannot supersede the device labeling. The applicant may choose to communicate with the manufacturer of the qualified article to modify the labeling for the article.

It may be possible that certain elements of this battery of testing can be combined with the biological tests noted in Section K in order to minimize testing.

Process Life Determination

A factor in all compatibility tests is the duration of compatibility, i.e., how many cycles an article can withstand before it fails or is otherwise unusable. Articles that are compatible with a sterilizer are those that retain their safety and effectiveness for their intended use after an acceptable number of reprocessing cycles. The acceptable number of cycles to failure can be correlated to the classified sterilizers or based on user preference. Unless there is adequate justification, in no case should an article fail when exposed to fewer cycles than possible with a classified sterilizer.

Data shall be submitted on the process life of the claimed compatible articles. In some cases, the test article may not exhibit significant, quantifiable deterioration after numerous cycles. If this is the case, the applicant may submit a justification for a projected compatibility of the material or device based upon analytical methods in order to minimize the extent of testing.

Functional Compatibility of Articles

Characterize the effect of repeated sterilization processes on the functionality of replicates of the representative test articles. The functionality parameters can be determined on the basis of use requirements, specifications of the device and the component materials. The methods of evaluation should be objective, whenever possible, e.g., tensile properties, flexural properties, impact resistance, hardness, compressive strength, burst strength, tear strength, color, dimensions, permeability, optical transmission, electrical resistance, etc.. The tests must incorporate simulated use conditions on the test articles between processes. There are extensive published test methods for each parameter and the applicant should refer to these methods in devising test protocols.

Biocompatibility of Component Materials

The applicant shall identify the test articles and the tests conducted on each article. The Tripartite Biocompatibility Guidance for Medical Devices should be used as a reference to identify the appropriate tests. The applicant should identify any other reference used for determination of tests. ISO 194 can be used as a reference.

For metals, some surface tests may be useful, e.g., SEM, contact angle. Identify any other surface or material degradation effects to include discoloration, corrosion, cracking, crazing, embrittlement, etc.

Q. Final Process Qualification

A summary of data from a final qualification test battery should be submitted. The qualification documentation submitted should include three consecutive runs times the variables of operation (e.g., three runs for each mode of operation) under worst case loading conditions indicated in labeling. Standard test packs should be used. The applicant must submit detailed documentation of failures and corrective measures and retests.

A summary of acceptance criteria should be submitted regarding process parameters, microbicidal effectiveness and processed device performance. Certification that the system performs in accordance with specifications should be provided.

R. Contacts and Addresses

General questions regarding the submission of premarket applications should be directed to the Division of Small Manufacturers Assistance at (800) 638-2041.

Questions regarding this guidance document should be directed to the following address:

FDA
Division of General and Restorative Devices (HFZ-410)
Infection Control Devices Branch
1390 Piccard Dr.
Rockville, MD. 20850
(301) 427-1307

S. Checklist

510(k)#:_____ Sponsor:_____
Date:_____ Reviewer: _____

#	Y/N	Element
1.		EPA Certification and Summary of Data
2.		References to Standards
3.		Labeling markings manual service manual
4.		Description design, construction, components process parameters process monitors software
5.		Cycle Overview
6.		Test Packs
7.		Comparison to Predicate
8.		Physical/Chemical Performance Tests
9.		Biological Test Battery screen F value D values 1/2 cycle and Total Kill Endpoint Simulated and In-Use Tests Summary
10.		Toxicity
11.		Residues
12.		Processed Device Qualification process life functionality biocompatibility
13.		Final Qualification

Attachment 1
Comparison Table

Feature	New Device	Predicate
EPA Registered Component Y/N		
Labeling/Intended Use		
Design, Construction, Components		
Process Parameters: time temp pressures, etc.		
Process Monitors: recorders gauges printouts, etc.		
Software/Firmware Controlled		
Cycle(s) Comparison		
Process Equivalent Time (for steam and dry heat)		

This table illustrates the type of comparisons that should be made, not necessarily the amount of information.