Guidance for Industry and FDA Reviewers

# Content and Format of Premarket Notification [510(k)] Submissions for Liquid Chemical Sterilants/ High Level Disinfectants

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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

GRZAN

# Preface

## Public Comment

Comments and suggestions may be submitted at any time for Agency consideration to Chiu S. Lin, Ph.D., CDRH, HFZ-480, 9200 Corporate Boulevard, Rockville, MD 20850. Comments may not be acted upon by the Agency until the document is next revised or updated. For questions regarding the use or interpretation of this guidance contact Chiu S. Lin, Ph.D. at (301) 443-8913 or by electronic mail at cxl@cdrh.fda.gov.

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# Content and Format of Premarket Notification [510(k)] Submissions for Liquid Chemical Sterilants/High Level Disinfectants[1]

## BACKGROUND

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

The FDA regulates the introduction of medical devices into interstate commerce. A person intending to market a liquid chemical sterilant/high level disinfectant for use on reusable heat sensitive critical and semicritical medical devices must submit a premarket notification [510(k)] submission to the FDA 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 and other regulatory requirements pertaining to the marketing of a new medical device are discussed in guidance documents available from the CDRH Division of Small Manufacturers Assistance (DSMA). This guidance document provides 510(k) applicants with specific recommendations regarding information and data to be submitted to the FDA in a 510(k) submission for liquid chemical sterilants/high level disinfectants.

The effective use of liquid chemical sterilants/high level disinfectants is important in preventing nosocomial infections. The use of comprehensive, scientifically sound criteria for the evaluation of liquid chemical sterilants/high level disinfectants is essential to help ensure that these agents are safe and effective for their intended use. The FDA recognizes the importance of providing applicants and other interested parties with the agency's 510(k) submission criteria for liquid chemical sterilants/high level disinfectants. This document facilitates the assembly of necessary data, maintains consistency of reviews, and provides for a more efficient regulatory process.

This guidance is predicated upon the legal principles of the 510(k) process. It also draws upon the long-standing regulatory and scientific basis for evaluation of germicides by other federal agencies. It is a product of interactions with interested parties in industry, government, and academia as well as with infection control and other health care professionals.

The Food Quality Protection Act of 1996 (FQPA) exempted liquid chemical sterilants (and the subordinate high level disinfectants) intended for use to process reusable critical and semicritical medical devices from the definition of a pesticide under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA).

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[1]This document is intended to provide guidance. It represents the Agency's current thinking on the above. It does not create or confer any 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.

The Environmental Protection Agency (EPA) no longer regulates such sterilants/high level disinfectants. The FDA now has sole regulatory jurisdiction over liquid chemical sterilants/high level disinfectants intended for use to process reusable heat sensitive critical and semicritical medical devices. For this reason, this document pertains only to liquid chemical sterilants/high level disinfectants used to process reusable heat sensitive critical and semicritical medical devices. This guidance document incorporates the provisions of the FQPA and the agreements between the FDA and the EPA.

The FDA incorporated comments on the content of this document, which were submitted to the FDA by industry, into this final document. This final document replaces FDA's 1992 guidance document, "Guidance on the Content and Format of Premarket Notification [510(k)] Submissions for Liquid Chemical Germicides," dated January 31, 1992 and other versions of the draft guidance document. Method development, research and discussions about the germicide evaluation process are ongoing. Therefore, this document is not static and will be revised periodically so that it remains current with state of the art developments in the field of infection control.

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# I. INTRODUCTION

## I.A. Scope

This document provides guidance concerning the content and format of 510(k) submissions for liquid chemical sterilants/high level disinfectants intended for the sterilization and/or high level disinfection of reusable heat sensitive critical and semicritical medical devices.

The Food and Drug Administration (FDA) encourages a sponsor to meet with FDA representatives prior to submitting a 510(k) for a liquid chemical sterilant/high level disinfectant to discuss germicide-specific protocols and preliminary data.

## I.B. Exclusions

This document EXCLUDES the following products:

1. an antimicrobial agent, such as ethylene oxide, that is a gas or chemical vapor at the time of use; these agents are used with sterilizing systems and are addressed in a separate guidance document (see "Guidance on Premarket Notification [510(k)] Submissions for Sterilizers Intended for Use in Health Care Facilities").

2. chemical germicide technology used only in a manufacturing setting

3. chemical germicides intended to disinfect contact lenses and hemodialyzers (A guidance document for germicides used for reprocessing hemodialyzers is in preparation.)

4. antimicrobials that are indicated for use on the body (antiseptics)

5. general purpose disinfectants per the definition set forth in the June 4, 1993 Memorandum of Understanding (MOU) between the FDA and the Environmental Protection Agency (EPA); The MOU is included as an attachment to the October 1993 draft document, "Guidance on the Content and Format of Premarket Notification [510(k)] Submissions for General Purpose Disinfectants," which is available from the FDA's Division of Small Manufacturers Assistance (DSMA, 1-800-538-2041).

## I.C. Definitions

1. *Bioburden (microbial load):* Population of viable microorganisms on a raw material, component, a finished product and/or a package (ANSI/AAMI/ISO 11134-1993); also known as "bioload" or "microbial load."

2. *Chemical indicator for a liquid chemical germicide:* A monitoring device designed to respond with a characteristic chemical reaction to the concentration of the active ingredient(s). Chemical indicators are intended to indicate a visible change ("pass" response) to the user when the minimum set concentration is present. Chemical indicators for liquid chemical germicides do not reflect other critical parameters, such as contact time and temperature, required to achieve sterilization or disinfection.

3. *Cleaning (or precleaning):* The removal, usually with detergent and water, of adherent visible soil, blood, protein substances, and other debris from the surfaces, crevices, serrations, joints, and lumens of instruments, devices, and equipment by a manual or mechanical process that prepares

the items for safe handling and/or further decontamination (AAMI, 1995).

4. *Death Rate Curve (or Survivor Curve):* The graphic representation of the microbial death rate kinetics for a specific microbicidal agent on a defined microbial population (AAMI, 1995).

5. *Decontamination:* Disinfection or sterilization of infected articles to make them suitable for use (Block, 1991).

6. *Disinfectant:* An agent that destroys pathogenic and other kinds of microorganisms by chemical or physical means. A disinfectant destroys most recognized pathogenic microorganisms, but not necessarily all microbial forms, such as bacterial spores.

7. *Disinfection:* The destruction of pathogenic and other kinds of microorganisms by physical or chemical means. Disinfection is a less lethal process than sterilization, since it destroys most recognized pathogenic microorganisms, but not necessarily all microbial forms, such as bacterial spores. Disinfection processes do not ensure the margin of safety associated with sterilization processes (AAMI, 1995).

8. *Germicide:* An agent that destroys microorganisms, especially pathogenic organisms. Other terms with the suffix -cide (e.g., virucide, fungicide, bactericide, sporicide, tuberculocide) destroy the microorganism identified by the prefix (Block, 1991).

9. *High Level Disinfectant:* A germicide that inactivates all microbial pathogens, except large numbers of bacterial endospores, when used according to labeling (Rutala, 1990; Spaulding, 1970). The FDA further defines a high level disinfectant as a sterilant used under the same contact conditions except for a shorter contact time.

10. *Inorganic and Organic Load:* The naturally occurring or artificially placed inorganic (e.g., metal salts) or organic (e.g., proteins) contaminants present on a medical device prior to exposure to a microbicidal process.

11. *Medical Device (as defined by the Food, Drug, and Cosmetic Act):* 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.
12. *Minimum Effective Concentration (MEC):* The minimum concentration of a liquid chemical germicide, which achieves the claimed microbicidal activity. The MEC is determined by dose response testing.

13. *Minimum Recommended Concentration (MRC):* The minimum concentration of a liquid chemical germicide at which efficacy has been demonstrated. The MRC is not necessarily an MEC as determined by dose response testing.

14. *Process Residue:* The substance remaining on a medical device after exposure to a decontamination, disinfection, or terminal sterilization process.

15. *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.

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

17. *Sterile:* State of being free from viable microorganisms (ANSI/AAMI/ISO 11134-1993).

18. *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).

19. *Sterilization:* Validated process used to render a product free of all forms of viable microorganisms (ANSI/AAMI/ISO 11134-1993).

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

21. *Unit:* A specified substrate or carrier upon which a 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 a test tube or Petri plate, an entire device, a component of a device (if the device must be disassembled prior to sterilization or disinfection), or a portion of a device.

22. *Verification:* Confirmation by examination and provision of objective evidence that specified requirements have been fulfilled (Section 820.3 of the FDA Quality System Regulation 1996).

23. *Vegetative State:* An active growth phase of an organism.

## I.D. Regulatory Authority and Classification of Liquid Chemical Germicides

The FDA regulates medical devices under authority of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The FDA classified medical devices that were in commercial distribution prior to the 1976 amendments to the FD&C Act for medical devices, or the so-called pre-amendments 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. Call the FDA's Division of Small Manufacturers Assistance (DSMA) at 1-800-538-2041 for guidance on general controls.

When the FDA classified the general hospital and personal use devices (45 FR 69678-69737, October 21, 1980), liquid chemical germicides were not included. At that time, the FDA regulated only those liquid chemical germicides with labeled indications for use on specific devices (e.g., hemodialyzers). Because the FDA considered liquid chemical germicides to be accessories to the devices they were used to process, the FDA regulated them in the same class as the primary device. Thus, the same liquid chemical germicide could be regulated as a Class I, Class II, and Class III device.

In the early 1990s, the FDA began actively regulating all liquid chemical germicides with health care indications. In order to avoid the potential problem of regulating the same product under multiple classes, the FDA decided to regulate liquid chemical germicides as a separate type of medical device and determined that these were unclassified devices. Additionally, the FDA adapted the terminology and classification scheme described by Spaulding (1970) for devices (i.e., critical, semicritical and noncritical) and the four levels of processing as proposed by the Centers for Disease Control and Prevention (CDC), sterilization, high level disinfection, intermediate level disinfection, and low level disinfection (Favero and Bond, 1993), to categorize medical devices.

Furthermore, the FDA developed criteria to support efficacy claims for the processing levels. The FDA defines a high level disinfectant as a germicide that demonstrates efficacy as a sterilant per results of the Association of Official Analytical Chemists (AOAC) Official Methods 966.04 Sporicidal Activity of Disinfectants (AOAC Sporicidal Test) at a longer contact time than that needed for high level disinfection. (This document discusses these criteria in greater detail later in Section III.H.) Therefore, the FDA defined three types of liquid chemical germicides for processing medical devices: sterilant/high level disinfectant, intermediate level disinfectant, and low level disinfectant. From a regulatory perspective, the FDA divided these products into two categories:

(1) liquid chemical sterilants/high level disinfectants for processing critical and semicritical devices

(2) general purpose disinfectants that include intermediate level disinfectants and low level disinfectants for processing noncritical devices and medical equipment surfaces

The EPA regulates liquid chemical germicides as pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). In an effort to ease the burden of this dual regulation, the FDA and the EPA signed a Memorandum of Understanding (MOU) (FDA, 1993; FDA, 1994) which gave the FDA primary responsibility for premarket efficacy and safety data review of liquid chemical sterilants/high level disinfectants and the EPA primary responsibility for premarket efficacy and safety data review of general purpose disinfectants. The MOU also provided interim procedures to eliminate dual efficacy and safety data reviews until completion of the EPA rulemaking process to exempt liquid chemical

sterilants/high level disinfectants from regulation under FIFRA and the FDA classification process to exempt general purpose disinfectants from 510(k) requirements.

In 1996, the Food Quality Protection Act (FQPA) exempted liquid chemical sterilants/high level disinfectants used to process critical and semicritical medical devices from the definition of a pesticide under FIFRA and no longer regulates them. The FDA now has sole regulatory jurisdiction over liquid chemical sterilants/high level disinfectants used to process reusable critical and semicritical medical devices. The FQPA did not affect the regulatory authority over general purpose disinfectants; therefore, the MOU remains in effect for these products and the dual regulatory requirements continue until the FDA classifies and exempts them from 510(k) requirements.

In an effort to complete the classification rulemaking process, the FDA convened the General Hospital and Personal Use Devices Panel (Panel) in July 1995 to classify liquid chemical sterilants/high level disinfectants and general purpose disinfectants. The FDA Panel recommended that liquid chemical sterilants/high level disinfectants be classified as Class II devices (general and special controls) and that general purpose disinfectants be classified as Class I devices (general controls) and be exempted from 510(k) requirements. The FDA accepted the Panel's recommendation and published this classification plan as a proposed rule in the Federal Register on November 6, 1998 (Volume 63, Number 215, pages 59917-59921). When the FDA publishes the final classification rule, the rule will exempt the general purpose disinfectants from the FDA 510(k) requirements. The FDA currently regulates liquid chemical sterilants/high level disinfectants in the same manner as Class II devices; therefore, this final classification rule will only codify the current regulatory process.

This guidance document pertains only to liquid chemical sterilants/high level disinfectants used to process reusable critical and semicritical medical devices, an replaces the 1992 guidance document for liquid chemical germicides. The October 1993 draft document, "Guidance on the Content and Format of Premarket Notification [510(K)] Submissions for General Purpose Disinfectants" is available to provide specific guidance for a 510(k) submission of general purpose disinfectants until they are exempted.

### I.E. Device Modifications

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

The following modifications are examples of changes that may be made to 510(k) cleared liquid chemical sterilants/high level disinfectants but do not require a new 510(k) submission:

1. changes in containers/closures based on data from the FDA accepted stability protocols in the original 510(k)

2. additions to lists of compatible materials in labeling based on data from the FDA accepted test regimen described in the original 510(k)

3. changes to cleared directions for use that only clarify the directions

4. addition of new precautions, warnings, contraindications, or adverse effects

5. reduction in (or narrowing of) tolerances for ingredient specifications

6. changes in source of raw materials

7. extensions of expiration date based on data from the FDA accepted protocols in the original 510(k)

Note: Under 21 CFR 807.85(b) a distributor of a specific germicide who markets the germicide under its own name and a repackager who places its own name on a germicide and does not change any other labeling or otherwise affect the device (e.g., change specifications or formulation) shall be exempt from 510(k) requirements if a premarket notification has been submitted for the specific germicide and previously found substantially equivalent, or the germicide is a pre-1976 germicide.

### I.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 the FDA at least 90 days before commercial distribution is to begin. Section 513(i) of the Act stipulates that the 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. In the document, "A New 510(k) Paradigm," (http://www.fda.gov/cdrh/ode/parad510.html) the FDA describes alternative approaches to the traditional method of demonstrating substantial equivalence. These alternative approaches are within the existing statutory framework, and it is anticipated that they will conserve the Agency's review resources while facilitating the introduction of safe and effective devices into interstate commerce. The first alternative, the "Special 510(k): Device Modification," utilizes certain aspects of the Quality System Regulation, while the second alternative, the "Abbreviated 510(k)," relies on the use of special controls and consensus standards to facilitate 510(k) review. See Appendices A and B for outlines of information to include in a Special 510(k) and Abbreviated 510(k), respectively.

## II. GENERAL PRINCIPLES REGARDING PRESENTATION OF DATA

A well written and organized submission facilitates the review process. The FDA recommends that the sponsor incorporate the following principles during preparation of their application.

### II.A. Editorial Considerations

1. Carefully edit and scientifically review the 510(k) submission.

2. Proofread the document to assure that all pages are properly indicated, consecutive, distinctly copied, and readable.

### II.B. Abbreviations

1. Use standard abbreviations acceptable to a peer reviewed journal wherever possible.

2. Identify all abbreviations at the beginning of each section in which they are used or in footnotes to tables and graphs.

### II.C. Data Availability

1. Retain data gathered during preparation of the 510(k) submission in a controlled and well-organized format so that it is readily available. Additional information or analysis is sometimes necessary for completing a review.

2. Bring errors to the FDA's attention immediately.

### II.D. Tables and Graphs

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.

### II.E. Published Literature

1. Summarize all referenced reports and data and explain how this information relates to the 510(k) submission.

2. Facilitate the review process by including references for published methods or data cited in submissions and reprints of other published reports or data.

### II.F. Protocols and Data Analysis

1. Provide the actual test reports that include the protocol (objectives, precise description of materials, experimental methods, controls), observations and statistical analyses, and the conclusions and comments on the test results. This guidance document addresses additional

specific directions on protocols in subsequent sections.

2. Clearly describe analytical methods and utilize recognized analytical and statistical methods. For statistical equivalence, please refer to Blackwelder (1982, 1995).

3. In each study report, specify if the study is in accordance with good laboratory practices (GLP) regulations (21 CFR Part 58) and explain any deviations.

**II.G. Submitting a 510(k)**

1. Submit a single 510(k) submission for a common product group, (e.g., same active ingredients and claims but different size containers). Other differences may require submission as separate 510(k)s and are considered on a case by case basis.

2. Include a response to all elements in Part III below or include an explanation for why data or information is not supplied, or for why the alternative information provided is sufficient. If after a cursory review, the FDA finds a 510(k) submission grossly incomplete, the FDA will refuse to accept the document and immediately delete it and then notify the applicant.

**II.H. Responding to a FDA Request for Additional Information**

Under 21 CFR Section 807.87(l), a 510(k) sponsor may amend their document to include additional information requested by the FDA that is necessary to reach a finding as to whether the device is substantially equivalent to a legally marketed device. The FDA may notify the sponsor by telephone and/or in writing of any additional information needed during the review. The FDA typically telephones sponsors to clarify minor deficiencies. Once the FDA notifies the applicant of deficiencies, the FDA places the 510(k) on hold. The FDA considers additional information submitted in response to an FDA request to be a supplement to the 510(k). The FDA encourages the sponsor to contact the FDA reviewer in the Infection Control Devices Branch before responding to deficiency letters to clarify or discuss the deficiencies.

1. Within 30 days of the request for additional information, elect to do one of the following:

   a. provide the requested additional information in writing to the Document Mail Center

   b. formally withdraw the 510(k) submission in writing to the Document Mail Center

   c. allow the submission to be deleted from the system by the FDA by not responding

2. Request limited extensions of the 30-day response period by submitting a written request to the Document Mail Center for an extension, clearly indicating the assigned 510(k) number and the additional time requested. The time period for the extensions is not open-ended and will be determined on a case by case basis. If the deficiencies are such that the FDA believes a firm cannot respond completely within 30 days, the FDA will notify the sponsor and immediately delete the 510(k) document.

3. In your response, clearly indicate the assigned 510(k) number on the supplemental information and include a restatement of the deficiencies (or append a copy of the deficiency letter) with a complete response. The FDA expects a response to address each issue identified in the deficiency letter and will not evaluate a grossly incomplete response. If you submit a less than comprehensive response, the FDA may place the file on hold again after notifying the sponsor or may raise new questions that must be addressed. Therefore, in order to minimize the review time, respond fully to requests for information.

## III. FORMAT AND CONTENT

### III.A. Cover Letter and Introductory Information

Consult the guidance document on the preparation of a Premarket Notification 510(k), available from the Division of Small Manufacturers Assistance (DSMA), before beginning work on the 510(k) document. This guidance document for liquid chemical sterilants/high level disinfectants is a supplement to the 510(k) guidance document. Include a cover letter clearly indicating, in a subject title, that it is a premarket notification [510(k)] submission. Include the following information as part of the cover letter or in separate sections:

1. the trade name or proprietary name of the device

2. the common, usual, or classification name of the device (e.g., liquid chemical sterilant/high level disinfectant)

3. the establishment registration number, if applicable, of the owner or operator submitting the 510(k)

4. the FDA product code: **MED**

5. the FDA review panel code: INCB

6. a classification statement (e.g., unclassified or Class II; see the Proposed Rule classifying liquid chemical sterilants/high level disinfectants as Class II devices)

7. for a chemical germicide that is indicated for use only with a specific reusable device (e.g., an endoscope), the name of the reusable device along with its FDA product code, if known

8. the name of the legally marketed predicate germicide(s) to which substantial equivalence of the device is claimed

9. the name, address, and telephone number of the individual or individuals who may be contacted regarding the submission; The FDA discusses the 510(k) only with those individuals designated by the firm as official contacts for the 510(k) submission.

### III.B. Table of Contents

Include a table of contents that notes the section titles and pages.

### III.C. Information Required by the Safe Medical Devices Act of 1990

Under the Safe Medical Device Act of 1990, a 510(k) must include either (1) a summary of the safety and effectiveness information in the 510(k) upon which an equivalence determination could be based [510(k) summary], or (2) a statement that safety and effectiveness information will be made available to interested persons upon request [510(k) statement]. In addition, persons who submit a 510(k) must certify that, to the best of their knowledge, all information is truthful and accurate and that no material fact has been omitted (Truthful and Accurate Statement).

The FDA delineates regulations establishing the requirements for the 510(k) summary, the 510(k) statement and the Truthful and Accurate Statement in 21 CFR 807.92, 807.93, and 807.87(k),

respectively. In addition, in accordance with the Center for Devices and Radiological Health (CDRH) policy, a 510(k) submission must include a statement of the device indications for use using a separate sheet of paper. Provide the following documents:

1. a 510(k) summary (see 21 CFR 807.92) or statement (see Appendix D)

2. the Truthful and Accurate Statement (see Appendix C)

3. an Indications for Use Statement (see Appendix E)

### III.D. Comparison of the New Germicide to the Predicate Germicide

Include a detailed summary table comparing the new germicide to the predicate germicide(s) with respect to physical and chemical properties, microbiology, toxicology, residues, reusable device compatibility, chemical indicators, and intended use (see 21 CFR 807.87(f)).

### III.E. Authorization for Data Access

1. If you cite data and/or information on file with another agency, include authorization from that agency for the FDA to access the data and/or information.

2. If you refer to data and/or information found in a device master file held by another firm, include documentation from the holder authorizing use of the file.

### III.F. Physical and Chemical Properties

#### III.F.1. Description of the Germicide

Provide the following information:

a. a statement of the product formula with tolerances as it is manufactured (e.g., in a format as provided in the Environmental Protection Agency (EPA) Confidential Statement of Formulation (CSF) for pesticides [see Appendix H]; other formats with the same information may also be used)

b. the upper and lower limits and nominal concentration for each ingredient in the final finished product; the upper limit is the maximum (and the lower limit is the minimum) amount of the ingredient that will be present in the product at any time while it is in commerce (i.e., over its shelf life)

c. the chemical name and Chemical Abstracts Service (CAS) number, of each active ingredient, intentionally added inactive ingredient, and any impurities that may be present in the product

d. the trade or proprietary name for all ingredients

e. the Material Safety Data Sheet (MSDS) for each component or ingredient

f. the purpose or function of each ingredient

g. a complete description of the product (e.g., single container germicide or a germicide with separate buffer and activator containers that are mixed prior to use)

h. the microbicidal mode of action of the final product formulation of the germicide, if known, with references

i. a thorough discussion of how the formulation was developed and how the specifications/ upper and lower limits were established - In the discussion, include the rationale for the presence and concentration of each ingredient. For example, explain the rationale from in vitro, simulated-use, and clinical-use tests (primarily stability, microbiology, and chemistry tests) that gauge factors such as the following:

1) expected inherent degradation of all ingredients during storage and use

2) potential dilution during reuse

3) inactivation by organic matter, oxidation and reduction of the active ingredients, exposure to heavy metals, etc.

4) added safety factors

5) pH buffering requirements and the buffering capacity of components

6) minimum effective concentration endpoint from dose response studies and/or minimum recommended concentration at which efficacy has been demonstrated, based on simulated- and in-use testing (Please refer to Section III.H.4 below for details on simulated- and in-use testing.)

**III.F.2. Accessory Devices or Containers/Closure Systems**

a. Identify any accessory devices or containers specified in the labeling for use with the sterilant/high level disinfectant for heating, aerating, etc.

b. Describe compatible materials for containers that may be used to hold the germicide during sterilization or disinfection of reusable medical devices.

c. In order to address the effect of the container/closures on the germicide stability, provide a complete description of the germicide container(s)/closure(s) including container sizes, identity of materials, and specifications.

d. A separate guidance document addresses endoscope reprocessors. (Call DSMA to obtain copies of the guidance document, "Guidance on Premarket Notification [510(k)] Submissions for Automated Endoscope Washers, Washer/Disinfectors, and Disinfectors Intended for Use in Health Care Facilities".)

**III.F.3. Stability Data**

Submit stability data obtained under the storage conditions and recommended use patterns specified in the labeling to support the following claims, as appropriate:

- the expiration date (shelf life) of the unopened marketed stock product(s)

- the use period of the opened and/or activated product
- the reuse life of a product with reusable claims

NOTE: Because this guidance addresses the stability of the microbicidal activity and toxicity of the product under the data requirements for efficacy and toxicity, these data need not be reiterated here.

a. **General Considerations for Stability Testing**

Because most liquid chemical sterilants/high level disinfectants are unstable at elevated temperatures, accelerated stability testing may not be appropriate. Therefore, stability studies should address the real time stability and dynamics of the formulation during storage, under conditions specified in the labeling, and during use of the product from an analytical chemistry perspective (i.e., any chemical/physical changes in the germicide expected or known, based upon analytical data).

1) Evaluate the chemical composition and physical properties of the germicide, such as color, odor, and clarity, and assess the suitability of the container.

2) Compare the pH and percentage amount of each active and inactive ingredient present in the product and activated solution at each time point with the initial specifications for the product.

3) Assess the presence and amounts of any impurities initially present or created in the stock or activated product during storage.

4) Address the effect of all possible neutralizing or interfering physico-chemical factors, such as temperature fluctuations, humidity, and light, on the stability of the product and the way in which these factors are controlled, as applicable.

5) For stability studies supporting the expiration date (shelf life) of the unopened container, store containers under the conditions indicated in the labeling and analyze samples of the unactivated and activated products throughout the test period.

6) For stability studies supporting the use period of a product after it is opened, store unopened containers under the conditions indicated in the labeling to the expiration date. Following the initial analysis, store the opened container to the end of the proposed use period under the conditions indicated in the labeling and handled in a manner that reflects actual use conditions of the product. For example, the storage conditions should reflect the product's sensitivity and exposure to the environment when the container is accessed repeatedly during the use period for removal of solution.

7) For stability studies supporting the use period of an activated product with no reuse claim, store unopened containers to the expiration date under the conditions indicated in the labeling. If applicable, then store the opened container to the end of the proposed use period under the conditions indicated in the labeling and handle it in a manner that reflects actual use conditions of the product. Following analysis of the unactivated product and activated product(s), store the activated product under the conditions indicated in the labeling to the end of the proposed use period, handled in a manner that

reflects actual use conditions of the product and then reanalyze the solution.

8) For studies supporting the reuse period, store unopened containers to the expiration date under the conditions indicated in the labeling. Following analysis of the unactivated and activated product(s), stress the activated product over the reuse life period using a simulated reuse protocol (e.g., the EPA reuse protocol). Then store and handle the product under conditions indicated in the labeling for the activated product and then reanalyze the solution.

9) Obtain stability data with each type of container and closure system proposed for marketing. For each type of container and closure system, include the largest and smallest size containers in the study. Establish the compatibility of the product for each container and closure system. Assess the possibility of interaction of leachables from the container with the product during storage. Evaluate each container and closure system to determine if the system remains intact and inert in the presence of the chemicals during the shelf life period under the stated storage conditions.

10) If a component of a germicide contains a microbiological preservative, then provide antimicrobial effectiveness data using microbial challenge tests, such as the USP Antimicrobial Preservative Effectiveness test, or by performing chemical assays for the preservative. At the minimum, conduct this testing at the beginning and end of the shelf life period, the use period, and the reuse life period, as applicable. If you use a chemical assay instead of an effectiveness test on an ongoing basis, then provide data correlating effectiveness with content at the end of the shelf life period.

b. **Sampling Plan and Times for Stability Testing**

1) Establish a sampling plan, including justification of sample size and the randomly selection method of sampling. To represent batch-to-batch variability, select containers from at least three different lots for each time point, and select each lot from a different production run. The test samples should represent the lot as a whole. For example, starting at a random point, select every nth container; the number of sampling times and the size of the lot determine n. Analyze at least two aliquots from each sample container.

2) Sample frequently enough so that any degradation can be characterized adequately and the nature of the degradation profile can be determined with reasonable assurance. For example, to determine the shelf life, analyze samples every three months for the first year, every six months for the second year, and then yearly thereafter. Sample more frequently if you expect a product to degrade rapidly or if little information is available to support the stability of the product.

3) For a new germicide not currently on the market, provide all available stability data that support the label shelf life. In lieu of complete stability data supporting the proposed claims, the FDA accepts a detailed protocol and sampling plan, as described below, for ongoing stability studies to be continued after clearance. Keep all stability data on file in accordance with the Quality System Regulation, 21 CFR Part 820.

4) Provide the following detailed information about the sampling plan, the test

protocols, the methods of verification, and the methods of analysis:

i) references to any standards, guidelines or regulations used as a basis for stability testing

ii) the initial, intermediate, and final composition and physical properties of the germicide

iii) any other analytical data, such as pH

iv) the storage conditions (that coincide with labeling)

v) the identification number and the manufacturing date of each lot

vi) the size of each lot

vii) the number of samples selected per lot

viii) the method used for selecting the samples

ix) the number of aliquots analyzed per sample

x) the method used for taking the aliquots

xi) the time points for analysis

xii) the dates of sampling and analysis

xiii) the duration of the study

xiv) calculations and the statistical analysis

xv) plots and graphs

xvi) any stability information from previous formulations obtained during product development or in the published scientific literature

### III.G. Labeling

### III.G.1. Introduction

Submit a draft of the label affixed to the germicide immediate container (bottle label) and any other draft labeling, such as a draft package insert containing additional information, that may accompany the germicide.

It is the primary responsibility of reusable device manufacturers to include verified reprocessing instructions in the labeling for their device, including use of compatible liquid chemical germicides, when appropriate. For information on validating device reprocessing instructions, see the April 1996 guidance document entitled, “Labeling Reusable Medical Devices for Reprocessing in Health Care Facilities: FDA Reviewer Guide,” available through DSMA.

The FDA is actively pursuing the improvement and harmonization of device labeling. The current reality is that labeling for many reusable devices does not include either reprocessing instructions or specifics on use of liquid chemical germicides. For this reason germicide labeling should stand alone by providing adequate directions for use to the user. Notwithstanding the current situation, all germicide labeling should refer the user to the reusable device labeling for additional directions.

**III.G.2. Background**

The FQPA exempted liquid chemical sterilants/high level disinfectants used on critical and semicritical devices from the definition of a pesticide under Federal Insecticide, Fungicide and Rodenticide Act (FIFRA). The EPA no longer regulates these products; the FDA is the sole regulatory authority. The EPA released Pesticide Regulation Notice, PR 98-2, advising registrants of the FIFRA provisions for liquid chemical sterilant products that are intended for use on critical and semicritical devices. The PR Notice states that no EPA references should appear in the labeling for FDA-regulated liquid chemical sterilants. Consult the PR Notice for additional guidance regarding label modifications stipulated by the EPA per the FQPA. Therefore, the EPA bottle label, previously utilized for liquid chemical sterilant/high level disinfection products, is no longer appropriate. Liquid chemical sterilants for other uses and general purpose disinfectants remain EPA-regulated.

Since the EPA and the FDA operate under different statutes, each agency adopted a different approach to regulating the labeling claims. The EPA's labeling regulation under FIFRA (Section 2(q)(2)(A)) as defined in 40 CFR Section 156.10 dictates the content and format of the bottle-affixed label for pesticide products. Hence, in 1991 when the FDA began actively regulating liquid chemical germicides, the agency chose not to change the EPA bottle labels to minimize regulatory confusion. The FDA recommended that manufacturers prepare a package insert bearing additional information for users about the use of liquid chemical germicides for reprocessing medical devices. The FDA described the recommended content of the package insert in its January 1992 draft guidance document for liquid chemical germicides. Consequently, the FDA-recommended package insert contains different information than the EPA-regulated bottle label. Although both pieces of labeling include abbreviated directions for use, indications for use, precautions, and warnings, only the FDA-recommended package insert includes contraindications, information on selecting germicides, detailed instructions for use, information on re-use and monitoring microbial activity of the product, and material compatibility.

The two agencies also use different terminology in their labeling. The FDA adopted the terminology used by the Centers for Disease Control and Prevention (CDC), which uses the Spaulding Classification scheme to describe the effect of germicides (i.e., low level disinfectant, intermediate level disinfectant, high level disinfectant, and sterilant), as shown below:

- Critical devices are introduced directly into the bloodstream or contact a normally sterile tissue or body space during use; sterilize these devices between uses.

- Semicritical devices contact intact mucous membranes and do not penetrate the blood barrier or otherwise enter normally sterile areas of the body; sterilize these devices between uses whenever feasible, but high level disinfection is minimally acceptable.

- Noncritical devices or instrument surfaces make only topical contact and do not penetrate intact skin; intermediate or low level disinfect these devices.

The EPA uses other terminology, such as hospital disinfectant, which is equivalent to a low level

disinfection claim, and hospital disinfectant with tuberculocidal activity, which is equivalent to an intermediate level disinfection claim. The EPA does not have a term that is equivalent to high level disinfection. In addition, the EPA allows a product to list on the label specific types of organisms (e.g., virucidal, fungicidal, etc.) against which the product is effective, while the FDA relies upon the broader disinfection terms, as defined by Spaulding, to indicate the product effectiveness. For example, the FDA's term "high level disinfectant" indicates that the product is virucidal, fungicidal, tuberculocidal, bactericidal, and able to kill some spores.

The agency believes that the label information and format should be consistent from product to product and should be consistent with the concepts and terminology used by the FDA, the CDC and the infection control community. Since the FDA has sole regulatory authority over these products, the agency now recommends that the bottle label contain all the essential information needed by the user for the safe and effective use of the product and that the package insert contain supplemental information for the user.

### III.G.3. Content of Labeling

The labeling for liquid chemical sterilants/high level disinfectants must comply with Section 801.5 of 21 CFR that requires adequate directions for use. Consult the labeling regulation before preparing product labeling. Manufacturers should provide clear, informative labeling to the healthcare community. Therefore, in addition to the information delineated in 21 CFR Sections 801.1, 801.4, 801.5, 801.6, and 801.15, the FDA recommends that the bottle and package insert contain the information described below. In the germicide labeling, refer the user to the reusable device labeling for detailed information on how to reprocess the device properly.

During the early 1990's when the products were in regulatory transition from the EPA, the FDA permitted a product to list on the label specific types of organisms (e.g., virucidal, fungicidal, etc.) against which the product is effective. These terms (virucidal, fungicidal, etc.) should be phased out and should not appear in the labeling for liquid chemical sterilant/high level disinfectant products now solely regulated by the FDA. Provide user information on microbial lethality in the package insert.

In addition, it has been a FDA labeling policy not to include references to specific diseases, such as AIDS, in advertising, labeling or supporting documents for a device unless effectiveness is proven by clinical trials.

### III.G.4. Bottle Label

Include information that is essential to the user in the bottle label. Clearly state the directions for use and the contact conditions. Include the following information on the bottle label:

a. **product name**

b. **contents, ingredients and nominal concentrations of active and inactive ingredient(s)**

c. **name and address of manufacturer and/or distributor**

d. **intended use**

Base each claimed level of germicidal activity on supporting potency, simulated-use and in-use test data and address each in the label. Make the user aware of the limitations of a

device sterilization claim for a liquid chemical germicide.

**Sample statements of intended use**

1) For a device high level disinfection claim supported by potency, simulated-use and in-use test data:

   "TRADE NAME is a high level disinfectant intended to disinfect reusable heat-sensitive medical devices which contact mucous membranes when used (state minimum recommended or effective concentration(s), contact time, temperature, etc.)."

2) For a device sterilization claim supported by potency, simulated-use and in-use test data:

   "TRADE NAME is a liquid chemical sterilant intended to sterilize reusable heat-sensitive medical devices which contact normally sterile areas of the body when used (state minimum recommended or effective concentration(s), contact time, temperature, etc.)."

e. **Warnings**

Describe any serious adverse reactions and potential safety hazards or limitations in use imposed by the germicide product. Include the steps that should be taken in case of contact with the germicide or presentation of a hazard.

f. **Precautions**

Identify any personal protective equipment that must be worn, facilities that must be used, and any other precautions the user should take to safely use the product. Include all materials, devices and other agents, such as cleaning agents that are not compatible with the germicide. Include statements similar to those shown below:

1) “Clean devices thoroughly prior to disinfection or sterilization to remove all blood and patient material that may inactivate the active agent. If all material is not removed, the germicide may not be effective and infection in the next patient may result.”

2) “Rinse devices thoroughly following disinfection or sterilization to remove toxic residues.”

3) “DO NOT use with the following heat-sensitive devices: [List any heat-sensitive devices that have been shown to be incompatible with the product.] Testing has shown that TRADE NAME is not compatible with these devices”

4) “DO NOT use with the following materials: [List materials that have been shown to be incompatible with the product.] Testing has shown that TRADE NAME is not compatible with these materials”

5) “DO NOT use with any heat-stable devices. Due to the inherent limitation of using liquid chemicals for sterilizing medical devices, TRADE NAME is limited to reprocessing only critical devices that are heat-sensitive and incompatible with other sterilization methods.”

6) “DO NOT use beyond XX days even if the concentration of the active agent(s) is above the Minimum Recommended (or Effective, as applicable) Concentration as indicated by

the recommended monitoring system. Do not rely solely on days in use. Use patterns may reduce the established reuse life of the liquid chemical sterilant. The concentration of the active ingredient should be evaluated before each use with an appropriate chemical indicator."

g. **Contraindications**

State any contraindications. Contraindications are conditions under which the germicide should not be used because the risk of use clearly outweighs any possible benefit.

h. **Adverse Reactions**

Identify possible adverse reactions following exposure to the product.

i. **Adequate Directions for Use**

1) Detail the preparation and use of the germicide including type of acceptable diluent, the method of activation or dilution, and the acceptable covered container(s) for (re)use of the germicide (e.g., stainless steel, plastics, heat bath, etc.).

2) Provide general instructions for cleaning devices in preparation for sterilization or high level disinfection. Refer the user to the reusable device labeling for the manufacturer's recommendations for device decontamination.

3) Provide the directions for sterilization and/or high level disinfection of cleaned devices in the prepared solution. Inform the user of the necessary elements for the sterilant/high level disinfectant to be effective:

- clean the devices thoroughly
- immerse the devices in the solution
- use a solution that is at or above the minimum recommended or effective concentration of the active ingredient(s)
- use the solution according to the Directions for Use

4) Provide detailed rinsing and neutralizing instructions, when needed, including the type of rinse and duration and/or volume of rinse necessary to remove residues as determined from testing. Define the quality of the rinse water, such as pH, presence of dissolved organic material, water hardness, microbial content, and temperature, in the labeling. State any factors in the rinse water that could interfere with adequate removal of germicide residues from devices.

5) Provide directions for reuse of the solution, if applicable. Direct the user to monitor the solution before each use for the minimum recommended or effective concentration(s) of the active ingredient(s), time, pH, and temperature, as applicable. Emphasize the need for monitoring the concentration of the active ingredient(s) of the germicide preparation before each use and that the decision to use the germicide product should be based on the concentration of the active ingredient(s) and not the days in use. Include a

statement similar to the one shown below in the directions for use:

"TRADE NAME can be reused for XX days provided the required conditions for use (concentration of the active agent(s), pH, time, and temperature) exist based on monitoring with a chemical indicator, pH test kit, timer, and thermometer."

j. **Chemical Indicator**

Provide information about the chemical indicator that is to be used with the reusable product for monitoring the MEC or MRC of the product active ingredient(s) during the reuse period.

k. **Storage Conditions and Expiration Date**

1) State the expiration date of the stock solution.

2) State that the product should not be used after the expiration date. For a product that is opened repeatedly for removal of solution, state that the product (from an opened or unopened bottle) should not be used after the expiration date. For a product with reusable claims, state that the product, activated or unactivated, should not be used after the expiration date.

3) State the storage conditions of the stock solution, opened container, activated solution, and use-dilution, as applicable.

4) State the use period for the opened container, activated solution and use-dilution, as applicable.

l. **Trained Personnel**

Provide a statement noting that the user should be adequately trained in the reprocessing (decontamination and sterilization or disinfection) of medical devices and in the handling of toxic substances, such as liquid chemical germicides.

m. **Emergency and Additional Information**

Provide a telephone number for emergencies or for additional information.

n. **Disposal**

State the method for disposal of the germicide and any neutralizers. Direct the user to check local and state regulations for hazardous waste disposal procedures.

### III.G.5. Package Insert

In addition to the information described above for the bottle label, provide the following information in the package insert:

a. **Germicide Classification Scheme for Labeling Purposes**

Briefly describe the Spaulding classification scheme as adapted by the FDA. Because liquid

chemical sterilants/high level disinfectants are for use with critical and semicritical devices only, limit the discussion of the classification scheme to critical and semicritical reusable devices. For example, use the following statements:

- "Critical reusable devices must be sterilized between uses."
- "Semicritical reusable devices should also be sterilized between uses whenever possible, but at a minimum, high level disinfection is acceptable."
- "A sterilant is an agent that destroys all viable forms of microbial life, when used according to labeling."
- "A high level disinfectant is a germicide that inactivates all microbial pathogens, except large numbers of bacterial endospores, when used according to labeling."

b. **General Information on Selection and Use of Germicides for Medical Device Reprocessing**

Provide a general statement such as the following:

"Choose a germicide with the level of microbicidal activity that is appropriate for the reusable medical device. See the labeling for the reusable device or contact the reusable device manufacturer for further instructions."

c. **Material and Device Compatibility**

1) Note the materials that are compatible and incompatible with the germicide as determined from the literature and/or testing.

2) Describe the conditions under which material samples were tested.

3) Include a statement indicating that material sample testing may not reflect compatibility of the germicide with finished medical devices.

4) If types of medical devices are listed as compatible with the germicide, then describe the conditions under which the device(s) was/were tested and refer the user to the labeling of the reusable device for additional instructions.

d. **Mode of Action of Germicidal Activity**

Briefly describe what is known about the microbial mode of action of the final product formulation of the germicide.

e. **Precleaning Agent Compatibility**

Note any cleaning agents or cleaning methods that are compatible or incompatible with the germicide as determined from the literature and/or testing.

f. **Toxicology and Adverse Reactions**

Provide a brief toxicity profile of the final product formulation of the germicide and/or the active ingredient(s) and note possible adverse reactions following exposure to the product.

### III.H. Efficacy Data

ALL OF THE TESTS DESCRIBED IN THIS SECTION SHOULD ADDRESS THE WORST CASE COMPOSITION CONDITIONS AS DEFINED BELOW, UNLESS OTHERWISE NOTED.

### III.H.1. Introduction to Microbiological Qualification Tests

Using the data and information in a 510(k), establish that the subject germicide is substantially equivalent to a predicate germicide (i.e., it has the same intended use and is as safe and effective as a legally marketed predicate when used according to the labeling). The FDA recognizes the value of using comprehensive, scientifically sound performance review criteria in order to help ensure that these products are safe and effective for their intended use. To support high level disinfection and sterilization efficacy claims, the FDA recommends a three-tiered testing regime, including potency tests, simulated-use tests (tests of inoculated instruments) and in-use tests (tests of clinically-used instruments).

### III.H.2. Study Report Content

The FDA expects that the protocols and data submitted to support the effectiveness of liquid chemical sterilants/high level disinfectants meet the highest standards for valid scientific studies, that is, at least as rigorous as for publication in peer reviewed scientific journals. In general, include the following information in the study reports:

a. a clearly stated objective(s)

b. the study protocol including details on the reagents, apparatus and operating technique, such as the following:

   1) identity of the test organism according to American Type Culture Collection (ATCC) code or other means that will precisely specify its taxonomic identity and origin, and a brief culture history of each organism

   2) care and preparation of microbial test organisms and execution of resistance tests

   3) description of the germicide solution, such as age, lot number, whether or not it was “stressed,” concentration of the active ingredient(s), etc.

   4) complete inoculation protocol including the following information:

      - concentration of the organism in suspension
      - the number of organisms theoretically applied to the device
      - the number of organisms that can be recovered from the device
      - the sites of inoculation
      - the volume ratio of inocula to germicide for a suspension test

5) protocols for microbial recovery with verification data for the methods

6) protocols for quantitating the wash-off factor with verification data for the methods

7) protocols for neutralization of the germicide with verification data for the methods

8) culture/subculture media and other solutions

9) glassware, dishes, bottles, and other apparatus

10) incubation devices, conditions, and procedures

11) organism transfer devices

12) exposure conditions (duration, temperature, pH)

13) description of any carriers

14) all controls

c. detailed results, thoroughly analyzed, with graphs and tables

d. summaries of the findings that are supported by the test results

Demonstrate the reproducibility of each test method or reference a standard test. Explain all variances from the reference tests. Thoroughly analyze the data and include statistical evaluations whenever possible. The FDA recommends that the protocols be designed with sufficient samples and replicates to ensure statistical significance at the 5% level with statistical power of at least 90%.

**III.H.3. Potency Tests**

Potency tests are conducted to demonstrate the potential use of the products for high level disinfection or sterilization of medical devices by establishing a broad spectrum of microbicidal activity of the test germicide. The potency tests recommended in this document are standardized benchmark tests that allow products to be compared one to another. For all potency testing, demonstrate product performance under worst case conditions and according to the labeled recommendations for use, reuse, etc., as described below:

a. Verify the germicide effectiveness under worst case conditions, including temperature extremes, and other factors as appropriate, such as light, which may affect the efficacy of the germicide.

1) Worst case conditions for a <u>single use</u> germicide - a germicide from a production run, stored to expiration and at its minimum specifications (diluted, if necessary).

2) Worst case conditions for a <u>reused</u> germicide - a germicide from a production run, stored to expiration, stressed to the end of its claimed reuse life, and diluted to its minimum recommended or effective concentration, if necessary. Incorporate into the simulated reuse protocol any factors that may impact the performance of the germicide, such as an

organic load, dilution, water quality, temperature variation, and pH changes.
NOTE:

- The EPA Re-use Test Protocol is an example of a simulated reuse protocol.
- If product that has been stored to the end of its shelf life is not available, contact the FDA to discuss the use of the oldest product available for testing.

### III.H.4. Simulated-Use and In-Use Tests

a. **Introduction**

A chemical germicide can be effective as a high level disinfectant or sterilant only if it comes in contact with the surfaces of a contaminated device and when the required contact conditions of time, pH, temperature, and any other critical variables are met. Potency tests demonstrate the potential use of the sterilant for sterilization or high level disinfection of medical devices. Simulated-use tests, on the other hand, help determine the penetrating capability of the germicide and other factors that prevent or limit contact and effectiveness of the germicide, i.e., the tests help identify conditions under which the germicide will fail. Simulated-use tests are **controlled tests that allow the precise application of a specified and quantified inoculum to selected device surfaces**.

Simulated-use testing intends to establish an adequate safety margin for the use of the product in/on actual medical devices. Some device designs are difficult to adequately clean and some device designs and materials favor biofilm formation on devices, complicating cleaning (Kaczmarek, et. al., 1992; Costerton, 1997). This test helps to establish more refined contact conditions for high level disinfection or sterilization of devices.

Because a simulated-use test on the performance of medical devices is a laboratory method, it cannot anticipate all outcomes during clinical use. Therefore, the FDA recommends in-use tests to confirm the results of simulated-use testing. The FDA believes that the persistence and resistance of ambient bioburden, such as biofilms, including wild microbial strains and other unforeseen factors, may impact the effectiveness of the germicide and limit correlation of simulated-use tests to actual use conditions.

b. **Content tips**

1) Report all available and relevant simulated-use or in-use performance data, both positive and negative, such as studies conducted by the applicant, data published in the scientific literature, and studies by reusable medical device manufacturers.

2) Summarize the data and justify how the data support a finding of substantial equivalence.

3) Demonstrate that the germicide, when used according to label contact conditions, meets labeling sterilization and/or high level disinfection claims under both simulated-use and in-use conditions.

4) Comparative tests conducted with the predicate device may not be needed. If special circumstances arise, the FDA may request additional testing with the predicate device.

5) Document all failures and analyze each for causation.

6) The labeling (e.g., limitations on use, adjustments to conditions of use, precautions, etc.) should reflect the findings of the simulated-use and in-use tests.

7) If verified reprocessing instructions are available, provide the reusable device labeling to confirm that labeling refers to the subject germicide (by trade name or type), and to confirm that comprehensive instructions exist (how well the germicide and device labeling mesh). When labeling for a reusable device includes verified reprocessing instructions, then redundant simulated-use and in-use tests by the germicide manufacturer on these reusable devices may not be necessary. In this case, germicide labeling can refer the user to the reusable device labeling for more specific instructions. Refer to the April 1996 guidance document, "Labeling Reusable Medical Devices for Reprocessing in Health Care Facilities" for further instructions (available from DSMA).

c. **General Considerations of Testing**

Include the following elements in the test battery for simulated- and in-use studies:

1) Incorporate devices with configurations that impede cleaning and penetration of germicides (e.g., small lumens, mated surfaces, and hinges). In lieu of these device features, or in case of sterilization or disinfection failures, the labeling should exclude use of the germicide on devices with these features.

2) Incorporate devices with the type of materials indicated in labeling as compatible.

3) Test replicate devices to obtain reliable results. Use a sufficient number of samples and replicates to ensure confidence in the results, if statistical testing methods are not to be used. Submit a rationale for the number and type of reusable devices selected.

4) Provide a description of the verified microorganism recovery method.

- Identify the minimum number of organisms that can be detected by the recovery method.

- Demonstrate that the media will support abundant growth when inoculated with low numbers of the test organisms, whether normal (10 cfu or less) or injured (100 cfu or less).

- Verify that the incubation period is adequate to allow for growth.

- Verify that the neutralization method has no germicidal effect and does not otherwise interfere with the microbicidal activity of the germicide.
- Use the same lot of media throughout testing. If a new lot of media is introduced, reverify the test method.

- Demonstrate a recovery of at least 90% of the injured organisms with the media.

5) Submit test reports indicating the compatibility of the germicide with any cleaning and

defoaming agents indicated in labeling of reusable medical devices.

6) Include appropriate concurrent controls.

The FDA recommends that you use the germicide lots used in the AOAC Sporicidal Test for the simulated- and in-use studies.

d. **Simulated-use Testing**

Consider the following additional elements when planning and conducting simulated-use testing:

1) Test semicritical devices, such as flexible endoscopes, to support a high level disinfection or sterilization claim. If the labeling indicates the use of the sterilant with specific devices, then test those devices.

2) Incorporate other factors into the test that impede cleaning and germicide activity, e.g., a representative inorganic and organic challenge added to the inoculum. Include an organic challenge representative of the type of worst case organic load to which the device is exposed during actual use, such as serum, blood, and secretions, and may remain associated with the device following cleaning. Although 5% BSA and hard water are commonly referenced as examples of organic and inorganic challenges, respectively, provide justification for their use in simulated-use testing. Consult the FDA for further information about what type of challenge to use in simulated-use testing.

3) Describe the microbial challenge and the device inoculation method in detail. Inoculate the most difficult areas for the germicide to penetrate and contact and then allow the inoculated device to dry. Quantify the inoculum on the device and the wash-off factor to determine the actual challenge to the germicide.

4) Stress and age the germicide solution and dilute the solution to its MRC or MEC, if necessary. Following exposure to the solution for the sterilization or high level disinfection contact time noted in the labeling, remove the test device and rinse, brush, and then rinse again according to the verified organism recovery method. Culture all rinses and brushes with the growth media that has been shown to support growth of low numbers of organisms.

e. **In-use Testing**

Conduct in-use testing in a clinical setting using multiple devices and in conjunction with the facility personnel who have been instructed to clean the device according to the reusable device label or the hospital protocol, when they are more specific. Direct the personnel to reprocess and rinse the test devices according to germicide label instructions. Employ no extraordinary methods of device preparation prior to exposure to the germicide, and conduct testing using fresh solution or under worst case conditions. Use the germicide solution as described in the labeling. Quantify the microbial challenge on a representative control device before and after cleaning the control devices.

If the processed reusable devices are retreated with a legally marketed germicide before being returned to service, then in-use testing of germicides in health care facilities can be

considered nonsignificant risk studies under 21 CFR Part 56, which do not require prior FDA approval under the Investigational Device Exemption (IDE).

### III.H.5. High Level Disinfection Claim

Support the high level disinfection claim with efficacy data from potency tests and with simulated– and in-use tests as outlined below.

#### a. Potency Tests

1) FDA defines a high level disinfectant as a sterilant used under the same contact conditions except for a shorter contact time. Therefore, products with high level disinfection claims should first qualify as a sterilant by passing the Association of Official Analytical Chemists (AOAC) Sporicidal Test (Sporicidal Activity of Disinfectants, AOAC 6.3.05:1995, Official Method 966.04) as a sterilant, i.e., no failures in the full test with three separate product lots and under worst case conditions of germicide composition (as defined in Section III.H.3.a) when used according to labeling. Please note that the FDA will not accept partial AOAC Sporicidal Activity tests.

- Submit a study report showing the results of complete testing. In the testing, include 60 carriers, representing each of two types of surfaces (porcelain penicylinders and silk suture loops). Test a total of 720 carriers or 240 carriers per product sample. Test the germicide against spores of both *Bacillus subtilis* ATCC 19659 and *Clostridium sporogenes* ATCC 3584 on three product samples representing three different batches. Use a contact time in the test that is comparable to the sterilization contact time for the claimed predicate germicide.

- Obtain results of confirmatory tests conducted by an independent laboratory using one of the three lots used in the initial AOAC Sporicidal tests. When the FDA began actively regulating liquid chemical germicides in the early 1990's, we recommended efficacy testing that was consistent with the EPA efficacy data requirements for sterilizing or sporicidal agents (EPA DIS/TSS-9, July 11, 1985). Because precedence has been established, the FDA continues to recommend that the AOAC Sporicidal Test be conducted with a total of 720 carriers as described above.

- Compare the AOAC Sporicidal Test contact times of the tested germicide and a legally marketed germicide consisting of a similar active ingredient. If there are significant differences between the contact times of the claimed predicate germicide and the new germicide, provide scientific justification, such as survivor curve analysis and the supporting data. Provide justification for the contact times by considering the practicality, material compatibility and microbicidal activity of the germicides.

- Perform the AOAC Sporicidal Test as written in the most recent edition of the standard test recognized by the FDA. In a few special cases, a sponsor may consider deviations from the AOAC test, if they are scientifically justified. Consult the FDA prior to initiation of such testing.

2) Once the product qualifies as a sterilant, conduct an additional potency test using the same contact conditions used for the AOAC Sporicidal Test except at a shorter contact

time, as recommended in the labeling, in order to determine the time required to kill $10^6$ organisms of an appropriate mycobacterium species, i.e., *Mycobacterium bovis* or *Mycobacterium terrae*. Use an alternative representative mycobacterium species if you can demonstrate with test data or literature references that the resistance of the organism to the chemical is similar to *Mycobacterium tuberculosis* var. *bovis*. The FDA recommends the modified (quantified) Tuberculocidal Activity of Disinfectants (AOAC 6.3.06:1995, Official Method 965.12) or a quantitative suspension test (Ascenzi et al., 1987).

- Conduct testing with the mycobacterium in suspension or on carriers, but quantify the number of organisms on the carriers.

- Run control carriers concurrently with the test group.

- Conduct testing with two of the three lots of product used for the AOAC Sporicidal Test.

3) Submit study reports describing the microbiological lethality profile of the germicide under worst case conditions of germicide composition (See III.H.3.a). Use a contact time in each test shown below that is comparable to the contact time for the claimed predicate germicide. The proposed high level disinfectant should pass the following additional tests under the test conditions defined in the method noted:

- Fungicidal Activity of Disinfectants Using *Trichophyton mentagrophytes* (AOAC 6.3.02:1995, Official Method 955.17) - Conduct testing with one of the three lots of product used for the AOAC Sporicidal Test.

- Testing Disinfectants Against *Salmonella choleraesuis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, Use-Dilution Methods (AOAC 6.2.01:1995, Official Methods 955.14, 955.15, and 964.02) – Conduct testing with one of the three lots of product used for the AOAC Sporicidal Test.

- Virucidal Tests previously recommended by the EPA for its germicide registration program (DIS/TSS-7, November 12, 1981) – Conduct testing with one of the three lots of product used for the AOAC Sporicidal Test.

For a list of the FDA recognized voluntary standard methods and supplemental information on these standard methods see http://www.fda.gov/cdrh/modact/steril.html. If testing was conducted according to these protocols, the firm may declare conformity to the recognized standard method and state any deviations from the standards that may apply (see Abbreviated 510(k) as described in Appendix B).

b. **Simulated-use Testing**

See Section III.H.4 for information about simulated-use testing. Use the most resistant mycobacterium species as the test organism. To support a high level disinfection claim, a test germicide should be able to kill at least $10^6$ inoculated mycobacteria under the recommended contact time. For example, the FDA expects no survivors if the test device is challenged with a 6 log inoculum of mycobacterium. If failures occur, document and analyze each failure for causation, and then reevaluate the proposed label contact conditions for

the high level disinfection claim.

c. **In-use Testing**

See Section III.H.4 for information about in-use testing. Conduct in-use testing according to the label contact conditions for device high level disinfection. The FDA expects no surviving organisms from devices used for testing. If failures (i.e., surviving organisms recovered) occur, document and analyze each failure for causation, and then reevaluate the proposed label contact conditions for the high level disinfection claim.

### III.H.6. Sterilization Claim

The survival kinetics for thermal sterilization methods, such as steam and dry heat, have been studied and characterized extensively, whereas the kinetics for sterilization with liquid chemical sterilants are less well understood. The information that is available in the literature suggests that sterilization processes based on liquid chemical sterilants, in general, may not convey the same sterility assurance level (SAL) as sterilization achieved using thermal or physical methods (Spaulding, 1971; Favero, 1995). The data indicate that the survival curves for liquid chemical sterilants may not exhibit log-linear kinetics and the shape of the survivor curve may vary depending on the formulation, chemical nature and stability of the liquid chemical sterilant. In addition, the design of the AOAC Sporicidal Test does not provide for quantification of the microbial challenge. **Therefore, sterilization with a liquid chemical sterilant may not convey the same sterility assurance as other sterilization methods.**

One of the primary differences between thermal and liquid chemical processes for sterilization of devices is the accessibility of microorganisms to the sterilant. Heat can penetrate barriers, such as biofilms, tissue, and blood, to attain organism kill, whereas liquids cannot adequately penetrate these barriers. In addition, the viscosity of some liquid chemical sterilants impedes their access to organisms in the narrow lumens and mated surfaces of devices (Muscarella, 1998). Another limitation to sterilization of devices with liquid chemical germicides is the post-processing environment of the device. Devices cannot be wrapped or adequately contained during processing in a liquid chemical sterilant to maintain sterility following processing and during storage. Furthermore, devices may require rinsing following exposure to the liquid chemical sterilant with water that typically is not sterile. Therefore, due to the inherent limitations of using liquid chemical germicides for sterilizing medical devices, the FDA recommends that liquid chemical sterilants be limited to reprocessing only critical devices that are heat-sensitive and incompatible with other sterilization methods.

The FDA believed at the time it began actively regulating liquid chemical sterilants/high level disinfectants that these solutions were primarily used for high level disinfection of devices and were only rarely used for sterilization of devices. Therefore, the FDA accepted device sterilization claims based only on AOAC Sporicidal Test data, as allowed by the EPA for sterilant registration. It now appears that an increasing number of germicide manufacturers intend to recommend their products for sterilization of heat-sensitive critical and semicritical devices. Therefore, the FDA now recommends that simulated-use testing with a calibrated bacterial spore inoculum suspended in an organic/inorganic challenge and actual-use testing be conducted to support a device sterilization claim. Establish the recommended conditions for device sterilization by liquid chemical sterilants as described below:

a. **Potency Tests**

1) Submit a study report showing that a germicide formulation claimed as a sterilant

passes the AOAC Sporicidal Test as a sterilant as described in Section III.H.5.a.1.

2) Submit study reports describing the microbiological lethality profile of the germicide. The proposed sterilant, used under worst case conditions for germicide composition, should pass the following additional tests under the conditions defined in the method noted:

- Modified (quantified) Tuberculocidal Activity of Disinfectants (AOAC 6.3.06:1995, Official Method 965.12) or a quantified suspension test (Ascenzi, 1987) – Conduct testing with two of the three lots of product used for the AOAC Sporicidal test. (See Section III.H.5.a.2)

- Fungicidal Activity of Disinfectants Using *Trichophyton mentagrophytes* (AOAC 6.3.02:1995, Official Method 955.17) – Conduct testing with one of the three lots of product used for the AOAC Sporicidal Test.

- Testing Disinfectants Against *Salmonella choleraesuis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*, Use-Dilution Methods (AOAC 6.2.01:1995, Official Methods 955.14, 955.15, and 964.02) – Conduct testing with one of the three lots of product used for the AOAC Sporicidal Test.

- Virucidal Test previously recommended by the EPA for its germicide registration program (DIS/TSS-7, November 12, 1981) – Conduct testing with one of the three lots of product used for the AOAC Sporicidal Test..

For a list of the FDA recognized voluntary standard methods and supplemental information on these standard methods see http://www.fda.gov/cdrh/modact/steril.html. If testing was conducted according to these protocols, you may choose to declare conformity to the recognized standard method and state any deviations from the standards that may apply (see Abbreviated 510(k) as described in Appendix B).

b. **Simulated-use Testing**

See Section III.H.4 for information about simulated-use testing. Use the most resistant spore-forming species, i.e., *Bacillus subtilis* as the test organism for simulated-use testing. To support a device sterilization claim, the test germicide should be able to kill at least $10^6$ challenge spores under the recommended contact time. Therefore, the FDA expects no survivors if the test device is challenged with an inoculum of 6 logs of spores. Document and analyze all failures for causation. **PLEASE NOTE:** A SAL **cannot** be inferred for a device sterilization claim based on this recommended testing protocol.

c. **In-use Testing**

See Section III.H.4 for information about in-use testing.

**For a product with a sterilization claim alone**, conduct in-use testing according to the label contact conditions for device sterilization. The FDA expects no surviving organisms from devices used for testing. If failures occur (i.e., surviving organisms recovered), document and analyze each failure for causation, and then reevaluate the proposed label contact conditions for the sterilization claim.

**For a product with both device sterilization and high level disinfection claims**, conduct in-use testing according to the label contact conditions for high level disinfection. The FDA expects no surviving organisms from devices used for testing. If no failures occur, then FDA may waive in-use testing at the longer contact time to support the device sterilization claim. If failures occur, document and analyze each failure for causation, and then reevaluate the proposed label contact conditions for the sterilization and high level disinfection claims.

### III.H.7. Summary of Microbiological Test Data

Provide a table summarizing the microbiological test section along with a comprehensive discussion of the findings of the tests and how the tests support the labeling claims.

## III.I. Biocompatibility

### III.I.1. Introduction

Germicide residues that remain associated with devices following reprocessing may be toxic and may pose a risk to patients and users. The residue may be the active ingredients, inert ingredients, by-products of the ingredients, neutralizer, or derivatives of the treated device. The amount of residue that remains may vary depending upon the conditions of use of the germicide, the specific component materials of the reprocessed device, and the methods used to reduce residuals prior to reuse. Therefore, it is important that the residues that remain associated with devices following reprocessing and rinsing are analyzed and quantified and that the potential health risks that these residues pose to patients are assessed. In addition, the user is exposed to the germicide solution while repeatedly processing devices with the germicide over a long period of time. Therefore, the potential health risks that the germicide solution poses to the user from handling the solution also should be assessed.

### III.I.2. Residue Data

a. If the labeling for certain reusable devices includes verified instructions for reducing germicide residues on the device to a safe level, then in the germicide labeling, refer the user to additional instructions in the reusable device labeling.

b. Because not all reusable devices include verified procedures for reducing residues to a safe level, provide comprehensive data regarding germicide residues remaining associated with processed devices. Expose representative devices to the germicide at the maximum specified use concentration for the maximum contact time indicated in the labeling before the items are rinsed.

c. Although a patient may be exposed to a device for only a very short time, no information currently is available to describe the rate at which residues may be released from devices during use. Therefore, the FDA takes a conservative approach and assumes that all residues remaining associated with a device are potentially available to the patient or user during exposure. The FDA recommends exhaustive extraction of residues from the entire device following reprocessing with the germicide product (including exposure and rinsing per the proposed product label).

d. Describe the residue extraction method and provide scientific justification for the method. Evaluate the type and amount of remaining residue according to the toxicological evaluation

discussed below. Quantify and evaluate the residues of all germicide ingredients or provide justification for why analysis of an ingredient is not necessary.

e. The list of materials tested need not be exhaustive, but include representative devices with component materials indicated in the labeling as compatible with the germicide. Test a range of devices that vary in surface area and configuration. The broader the scope of reusable devices indicated in the labeling, the more inclusive should be the test articles.

f. Base the information in the labeling (as noted in Section III.G.) upon these data. Thoroughly describe the residue reduction step (e.g., rinsing) for all labeled germicide use conditions. Do not recontaminate the processed reusable device during this step.

**III.I.3. Evaluation of Toxicity**

To ensure the safe use of the germicide product and of germicide-treated devices, assess the toxicity of the germicide solution and of all residues remaining on a reusable medical device following reprocessing with a germicide. This information assists the FDA in the evaluation of the potential health risks to patients and users exposed to the germicide residues and to users handling the germicide solution.

During evaluation of residues, consider both the active and inert ingredients. Identify the residues of concern and provide justification for excluding any residues. Provide evidence showing that the amount of each residue of concern remaining on a device is at a safe, nontoxic level.

To evaluate the toxicity of the germicide solution and the residues, review the available toxicity data for the germicide solution and of the identified residual chemicals. The data may be obtained from from toxicity studies sponsored by the manufacturers of the active and inert ingredients and from toxicity studies published in the scientific literature. Provide copies of all references. If adequate information is not already available, then conduct toxicity testing with the product at its maximum specified use concentration; alternatively, test the individual germicide product ingredients.

The FDA understands that liquid chemical sterilants/high level disinfectants are intended primarily for use on devices that contact the patient for a limited time (as opposed to implanted devices). To assess the toxicity of the residues, in general, the FDA notes the following tests using the germicide product and/or the individual ingredients:

- Skin irritation test
- Skin sensitization test
- Cytotoxicity test
- Acute dermal toxicity test
- Hemocompatibility/hemolysis test
- Subchronic dermal toxicity test

Use multiple dose levels of residue components to construct a dose-response curve to which the actual residue level can be compared during a risk assessment process. If the data from the above tests show that the use concentration is nontoxic, then one can assume that the device-associated residues are also nontoxic.

The FDA also uses the above tests, excluding cytotoxicity and hemocompatibility/hemolysis tests, to evaluate the toxicity of the germicide product and potential health risks to the user due to handling of

the germicide solution. The FDA suggests the following additional tests:

- Acute oral toxicity test
- Primary eye irritation test
- Acute inhalation toxicity test
- Genotoxicity tests
- Chronic toxicity test
- Reproductive and developmental toxicity tests

Depending on the results of the genotoxicity tests, carcinogenicity testing may also be indicated. Conduct all testing with the germicide product at its maximum specified use concentration.

Refer to the ISO 10993-1 and Office of Device Evaluation (ODE) Blue Book Memorandum #G95-1 for further details on biocompatibility testing of medical devices and to published guidelines and methods for conducting these tests. Provide a complete description of the toxicity test methods and cite, in each study report, any guidelines and methods used for conducting the tests.
If testing is conducted according to the FDA recognized consensus standards for biocompatibility testing, then declare conformity to the recognized standard method and state any deviations from the standards that may apply. (See the list of the FDA recognized consensus standards for biocompatibility and supplemental information at the CDRH internet site, http://www.fda.gov/cdrh/modact/recstand.html#Bio.)

### III.J. Device and Material Compatibility Qualification

#### III.J.1. Introduction

Liquid chemical germicides used to reprocess devices may damage the devices or lead to deterioration of the materials, and thus adversely affect the safety and effectiveness of the reprocessed device. For example, surface cracking or pitting makes the device more difficult to clean and may cause injury during use (Fuselier and Mason, 1997). In addition, clouding of the lens of an endoscope decreases visibility and thus the effectiveness of the device (Babb and Bradley, 1995). For these reasons, include data confirming the compatibility of the germicide with medical devices and component materials that are indicated in germicide labeling as compatible. The data should address the effects of the germicide on the functionality, material compatibility, and specifications of the claimed compatible medical devices and materials.

To evaluate the compatibility claims for devices/materials or general device and material classes described in the labeling, review the published literature or information from the device or material manufacturers for data supporting your compatibility claims. If the available data from these sources are inadequate, then conduct compatibility testing to support the germicide labeling claims. Provide information and/or test data that reflect the label claims for the germicide and the device. The labeling for a germicide may include claims of compatibility with general classes of materials (e.g., metals, polymers), general classes of devices (e.g., endoscopes), specific materials (e.g., polypropylene, stainless steel), specific devices (specific brand names), or any combination of the above claims.

For any specific reusable device claims, the germicide labeling cannot supersede the reusable device labeling. In the germicide labeling, refer the user to the reusable device manufacturer for specific reprocessing instructions. Do not identify specific reusable medical devices in the labeling as compatible with the germicide when the reusable device labeling specifically contraindicates its use. For example, labeling for dental handpieces contraindicates the use of liquid chemical germicides for

reprocessing the devices. Therefore, indicate in the germicide labeling that the use of the germicide with dental handpieces is inappropriate.

### III.J.2. Testing for Device/Material Compatibility

a. **Devices and materials to be tested**

Test the type of devices and materials that reflect the claims made in the germicide and reusable device labeling. If labeling for a reusable device indicates compatibility with the germicide, then there is no need to conduct redundant testing on that device, but in the germicide labeling, refer the user to the reusable device labeling. Also, direct the user to contact the germicide or reusable device manufacturer for further information.

If the labeling for the germicide indicates compatibility with specific materials, then test each material. When germicide labeling indicates compatibility with a specific class of articles (devices and/or materials), select test articles that are representative of the class and justify the selection.

The labeling defines the devices and materials that should be tested. Therefore, the broader the scope of devices and materials claimed in the labeling, the broader the potential testing that should be conducted. For example, reference to "metal" instruments, or simply "metals" connotes a range of material possibilities. The same is true regarding reference to "polymers" or "elastomers" rather than specific materials such as polyethylene.

b. **Process life or exposure time**

A factor in all compatibility tests is the duration of compatibility (i.e., the number of times a reusable device and material can be exposed to a germicide before it fails or is otherwise unusable). Devices and materials that are compatible with a germicide are those that are safe and effective for their intended use after a specified number of reprocessing cycles. The acceptable number of cycles depends on many factors such as use requirements.

Assessment of the process life of the devices and materials for compatibility with the germicide in part c below. Define an acceptable process life for each device and material and provide justification. The devices and materials should meet the process life requirements. In some cases, the devices and materials may not exhibit significant, quantifiable deterioration until after numerous cycles of reprocessing. In order to minimize the extent of testing, submit justification for the projected compatibility of the test article based upon extrapolations.

For compatibility testing, repeatedly expose the test devices to the germicide solution at the maximum specified use concentration for the maximum contact time indicated in the labeling.

c. **Reusable device analysis**

Characterize the effect of repeated processing on the functionality of replicate test devices. The FDA understands that the germicide manufacturer is not necessarily knowledgeable on the proper functioning of each reusable device and does not have access to the specifications for these devices and their component materials. Therefore, the FDA encourages the germicide 510(k) sponsor to work with reusable device manufacturers to evaluate the effect of repeated reuse of the germicide on the device functionality.

Although functionality testing on materials alone is conceivable, submit verification data showing that the test correlates to actual device use. The functionality parameters are determined primarily on the basis of specifications or functional requirements for the reusable device. The methods of functionality evaluation should be quantitative, wherever possible (e.g., tensile properties, flexural properties, impact resistance, hardness, compressive strength, color, dimensions, permeability, optical transmission, burst strength, tear strength, electrical resistance, etc.). Incorporate into the testing, simulated-use conditions of the test articles between processes. Visually examine evidence of material degradation which is characteristic of each material. For example, examine metals for discoloration, corrosion, cracking, crazing, and embrittlement.

Extensive published test methods for each parameter noted are available. Refer to the literature when devising test protocols. Describe the method of preparation of test devices/materials and methods and criteria for analysis of each parameter in the report.

### III.K. Chemical Indicators for Liquid Chemical Germicides

A chemical indicator for liquid chemical germicides is a monitoring device designed to respond with a characteristic chemical reaction to the concentration of the germicide active ingredient(s). Liquid chemical sterilants/high level disinfectants that are labeled for reuse can be used safely and effectively **only** if the user has a chemical indicator available to measure the level of active ingredient(s). If a germicide requires an indicator and no legally marketed indicator is available, The FDA will not find the germicide equivalent. A chemical indicator for a germicide that is marketed separately from the germicide requires the submission of a separate 510(k).

#### III.K.1. Description of the Chemical Indicator System

Include complete information on the physical and chemical properties of the chemical indicator. Provide the following information:

a. the formulation of the indicator system, including the name of each reactive and unreactive component and the quantity, proportion or concentration of each reactive ingredient

b. the purpose or function of each component

c. the chemical principle of the test system, including a diagram of the reaction

d. substances that interfere with the efficacy of the test system

e. a complete description of the packaging

f. a summary and explanation of the test, including the clinical utility, indications for use and significance of the test

#### III.K.2. Labeling for Chemical Indicators

Provide the following information in the package insert:

a. Intended Use - Identify the analyte or test objective and type of procedure, i.e., qualitative, semi-quantitative or quantitative.

b. Summary and Explanation of the Test - Include clinical utility, indications for use and significance of the test.

c. Chemical Principle of the Test Procedure - Include a diagram of the reaction.

d. Storage and Stability (as applicable) – Include the following information:

1) any limits on exposure to light, heat, moisture, strong acids, bases, heavy metals, etc.

2) the recommended storage conditions (e.g., temperature, humidity, etc.) for opened and unopened container, and caution user about variation in storage conditions

3) the expiration dates of the unopened and opened container

4) a statement that the indicator strip (from an opened or unopened bottle) should not be used after the expiration date

5) a space on the container for recording the date the container is opened

6) visible indications for reagent instability

e. Specimen Collection and Preparation

f. Assay Procedure - Include amount of sample required.

g. Materials Required - Identify materials provided and materials not provided.

h. Quality Control Procedures – Provide the following information:

1) commercially available products that should be used for positive and negative controls, if materials are not provided in the kit

2) frequency and levels of quality control

3) directions for interpretation of results of quality control material (satisfactory limits of performance)

i. Test Results Interpretation - Instruct the user how to determine the assay values by comparison with either a written description of the color or (preferably) a color chart.

j. Limitations – Provide the following information:

1) identity of any interfering substances

2) a caution for users who are color blind, when appropriate

k. Performance Characteristics - Provide the results of the comparison testing as described in part 4 below.

l. Warnings and Precautions – Provide the following information:

1) potential safety hazards, e.g., “Warning, Toxic Strips. Contain the following chemicals:…” and cautions regarding ingestion, eye exposure, etc.

2) a statement that chemical indicators cannot be relied upon or promoted as a means of verifying the sterilization or disinfection process; chemical indicators can only establish that a specific factor exists within the specified limits of performance of the indicator.

m. Selected Bibliography

### III.J.3. Performance Testing

Provide performance test data to support the labeling claim that the chemical indicator can accurately and reproducibly measure the MEC or MRC of the active ingredient(s) in the liquid chemical sterilant/high level disinfectant. Include the following information:

a. a detailed summary of the results obtained when comparing the performance of the chemical indicator with a predicate device or scientifically valid method for detecting the active ingredient of the germicide, utilizing split samples, and tested under simulated-use conditions - It is important that the testing demonstrate the failure point(s) for the chemical indicator in order to establish the margin of safety.

b. a description of the color development for the periods of time less than and longer than the time period specified for reading the results or justification as to why a description at such time points is not necessary

c. the protocol for determining the shelf life (expiration date) of indicators in unopened and opened containers under worst case storage and usage conditions as indicated in the labeling

### III.J.4. General Considerations for Performance Testing

a. Test replicate indicators to obtain reliable results. Use a sufficient number of samples and replicates to ensure confidence in the results. Submit a rationale for the number and type of indicators selected. The FDA recommends that a minimum of three lots be tested with 50-100 samples for each estimate in order to ensure confidence in the results, if statistical testing methods are not to be used.

b. Analyze the results of comparison testing according to the following characteristics:

1) Comparative Sensitivity - ratio of the number of true positives (TP) to the sum of the number of true positives and false negatives (FN) $\frac{TP}{TP + FN}$

2) Analytic Sensitivity - detection level of a test strip relative to a standard quantitative analytical test

3) Comparative Specificity - ratio of the number of true negatives (TN) to the sum of the number of true negatives and false positives (FP) $\frac{TN}{TN + FP}$

4) Analytic Specificity - extent to which a test strip reacts with one or more substances; identification of substances that could cause false positive results

5) Accuracy - agreement between an experimentally determined value and the accepted reference value

6) Precision - relative tightness of the distribution of measurements of a quantity about their mean value, expressed in terms of standard deviation

NOTE: For more information concerning sensitivity and specificity, please refer to Gail (1990). For more information concerning accuracy and precision, please refer to Mandel (1964).

c. Provide the specifications for the test such that the accuracy of a "Pass" or color indication of sufficient active ingredient falls entirely within the effective range of the active ingredient.

d. Demonstrate, with testing, the performance of the test system in the presence of possible germicide solution contaminants, such as detergents and organic and inorganic material. For example, conduct the testing using the worst-case germicide composition as described under Section III.H.3.a.

e. Conduct actual use testing for color and/or hue change analysis using test readers, as applicable.

## IV. CONTACTS AND ADDRESSES

Direct general questions regarding the submission of premarket notifications to the Division of Small Manufacturers Assistance at (800) 638-2041 or (301) 443-6597 or at http://www.fda.gov/cdrh/dsma/dsmamain.html

Direct questions regarding this guidance document to the following address.

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

Phone: (301) 443-8913

## V. 510(K) CHECKLIST

1. _____ Cover Letter (Signed and Dated)
2. _____ Table of Contents
3. _____ Indications for Use Form
4. _____ Truthful and Accurate Statement (Signed and Dated)
5. _____ 510(k) Statement **or**
6. _____ 510(k) Summary
7. _____ Comparison of Germicide to Predicate
8. _____ Physical and Chemical Properties
9. _____ Stability Data
10. _____ Labeling
11. _____ Potency Test Data _____ High level disinfection _____ Sterilization
12. _____ Simulated-use Test Data ____ High level disinfection _____ Sterilization
13. _____ In-use Test Data _____ High level disinfection _____ Sterilization
14. _____ Residue Data
15. _____ Toxicity Data
16. _____ Material/Device Compatibility Data
17. _____ Chemical Indicator Labeling
18. _____ Chemical Indicator Performance Data

## VI. APPENDIX A

### Special 510(k): Device Modification

A Special 510(k) is for manufacturers who intend to modify their own currently 510(k) cleared legally marketed liquid chemical sterilant/high level disinfectant. The manufacturer has determined that a new 510(k) is needed for the modification(s) and the modification does not affect the intended use of the device or the basic fundamental scientific technology of the device. The paradigm document (http://www.fda.gov/cdrh/ode/parad510.html) contains additional detail on eligibility criteria. The following modifications are examples of the types of changes to a 510(k) cleared liquid chemical sterilant/high level disinfectant that the FDA considers eligible for Special 510(k) submissions. These modifications are eligible provided test data demonstrate there is no significant change in contact conditions, stability, retention of residues, or material compatibility and there are no new claims associated with the changes.

a. addition, subtraction, or change in specifications of inactive ingredients

b. changes in containers/closures if product was cleared with incomplete stability data or if the original 510(k) does not contain an accepted stability protocol

c. increases in (or widening of) tolerances for active ingredient(s) specifications

d. elimination of any warnings, precautions or other safety related information

e. changes to manufacturing methods (same raw materials) that do not alter the cleared final product specifications

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

a. a coversheet clearly identifying the application as a “Special 510(k): Device Modification”

b. the name of the legally marketed (unmodified) device and the 510(k) number under which it was cleared

c. 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 Appendices C and D)

d. a summary of design control activities - Include the following information:

    1) 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

    2) 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

    3) 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.)

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

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

6) declaration of conformity with design controls (see Appendix F)

e. indications for use enclosure (see Appendix E)

## VII. APPENDIX B

**Abbreviated 510(k), Use of Consensus Standards, Special Controls, and Guidance.**

An Abbreviated 510(k) is for manufacturers who intend to market a new (not a modified) liquid chemical sterilant/high level disinfectant and who rely upon this guidance document as a special control and a standard recognized by the FDA. The paradigm document describes the recommended abbreviated documentation under this option in more detail. FDA maintains a list of recognized standards on the CDRH website at www.fda.gov/cdrh/modact/recstand.html. The list is updated at least annually.

Include the following information in an Abbreviated 510(k):

a. a coversheet clearly identifying the application as an "Abbreviated 510(k)"

b. 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 Appendices C and D)

c. summary information that relies on a guidance document an/or special control(s), a summary report that describes how the guidance and/or special control(s) were used to address the risks associated with the particular device type - (If a manufacturer elects to use an alternative approach to address a particular risk, sufficient detail should be provided to justify that approach.)

d. for a submission that relies on a recognized standard, a declaration of conformity to the standard – Submit the declaration in accordance with the following (see Appendix G):

    1) Identify any element of the standard that was not applicable to the device.

    2) 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.

    3) Identify any deviations from the standards that were applied.

    4) 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.

    5) Provide the name and address of any test laboratory or certification body involved and a reference to any accreditations of those organizations.

e. data/information to address issues not covered by guidance documents, special controls, and/or recognized standards

f. indications for Use enclosure (see Appendix E)

## VIII. APPENDIX C

PREMARKET NOTIFICATION
TRUTHFUL AND ACCURATE STATEMENT

*[Refer to Section 807.85(j)]*

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]*
---
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: _____*[Signed]*_____

_____*[Date]*_____

## X. APPENDIX E

INDICATIONS FOR USE STATEMENT

510(K) Number: (if known)

Device Name: [*Brand Name*]

Indications For Use: The [*Brand Name*] is used for…

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

Concurrence of CDRH, Office of Device Evaluation (ODE)

Prescription Use _____ OR Over-The-Counter Use _____

*(Per 21 CFR Section 801.109)*



GRZAN

## 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]*<br>*[Title]*<br>*[Company]* | *[Date]* |

### 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]*<br>*[Title]*<br>*[Company]* | *[Date]* |

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

## XII. APPENDIX G

DECLARATION OF CONFORMANCE 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.

*[signature]*
*[Name]*
*[Title]*

*[Date]*
Date

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

Attached is a sample EPA Confidential Statement of Formula.

*Confidential Business Information: Does Not Contain National Security Information (E.O. 12065)*

Form Approved. OMB No. 2070-0060 Approval expires 2-28-95

| United States Environmental Protection Agency, Washington, DC 20460 | A. ☐ Basic Formulation ☐ Alternative Formulation | B. Page ____ of ____ | See Instructions on Back |
|---|---|---|---|

## Office of Pesticide Programs (7505C) - Confidential Statement of Formula

| 1. Name and Address of Applicant/Registrant *(Include ZIP Code)* | 2. Name and Address of Producer *(Include ZIP Code)* | | |
|---|---|---|---|
| 3. Product Name | 4. Registration No./File Symbol | 5. EPA Product Mgr/Team No. | 6. Country Where Formulated |
| | 7. Pounds/Gal or Bulk Density | 8. pH | 9. Flash Point/Flame Extension |

| EPA USE ONLY | 10. Components in Formulation *(List as actually introduced into the formulation. Give commonly accepted chemical name, trade name, and CAS number.)* | 11. Supplier Name & Address | 12. EPA Reg. No. | 13. Each Component in Formulation a. Amount | 13. b. % by Weight | 14. Certified Limits % by Weight a. Upper Limit | 14. b. Lower Limit | 15. Purpose in Formulation |
|---|---|---|---|---|---|---|---|---|
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| | | | | | | | | |
| 16. Typed Name of Approving Official | | | | 17. Total Weight | 100% | | | |

| 18. Signature of Approving Official | 19. Title | 20. Phone No. (Include Area Code) | 21. Date |
|---|---|---|---|
| | | | |

EPA Form 8570-4 (Rev. 8-94)

White - EPA File Copy (original) Yellow - Applicant

## XIV. REFERENCES


1. ANSI/AAMI/ISO 11134-1993 Sterilization of Healthcare Products – Requirements for Validation and Routine Control – Industrial Moist Heat Sterilization.

2. Ascenzi, JM, Ezell, RJ, and Wendt, TM. A more accurate method for measurement of tuberculocidal activity of disinfectants. Appl. Environ. Microbiol. 1987; 53:2189-2192.

3. Association for Advancement of Medical Instrumentation (AAMI) Standards and Recommended Practices: Volumes 1 and 2: Sterilization, 1995 Edition.

4. Babb, JR and Bradley, CR. Endoscope decontamination: Where do we go from here? J. Hosp. Infect. Suppl. 1995; 30:543-551.

5. Blackwelder WC. Proving the null hypothesis in clinical trials. In: Controlled Clinical Trials. 1982; 3:345-353

6. Blackwelder WC. Similarity/equivalence trials for combination vaccines, combined vaccines and simultaneous administration. Annals of the New York Academy of Sciences, 754; May 31, 1995.

7. Block SS. Definition of terms. In: Disinfection, sterilization and preservation. Fourth ed. Philadelphia: Lea and Febiger, 1991:18-25.

8. Costerton, WJ. Cleaning techniques for medical devices: Biofilms 1997; Biomed. Instru. Technol. May/June:222-249.

9. Favero, MS. Chemical germicides in the health care field: The perspective from the Centers for Disease Control and Prevention. In: Rutala, WA (Ed.) Chemical Germicides in Health Care International Symposium, May 1994.Washington, DC: Association for Professionals in Infection Control and Epidemiology, Inc., and Morin Heights, P.Q., Canada: Polyscience Publications, Inc. 1995; pp. 33-42.

10. Favero, MS and Bond, WW. The use of liquid chemical germicides. In: Morrissey, RF and Philips, GB (Eds) Sterilization Technology: A Practical Guide for Manufacturers and Users of Health Care Products. New York: Van Nostrand Reinhold. 1993; pp309-334.

11. Favero, MS and Bond, WW. Chemical disinfection of medical and surgical materials. In: Disinfection, sterilization and preservation. Fourth ed. Philadelphia: Lea and Febiger, 1991:pp. 517-531.

12. Favero MS and Bond WW. Sterilization, disinfection, and antisepsis in the hospital. In: American Society for Microbiology, Manual of Clinical Microbiology, Washington, DC: 1991:183-200.

13. The Food Quality Protection Act of 1996; Pub. L. No. 104-170, 110 Stat. 1489 (1996).
14. Fuselier, HA and Mason, D. Liquid sterilization versus high level disinfection in the urologic office. Adult Urology. 1997; 50:337-340.

15. Gail MH. Some statistical methods for immunodiagnostic cancer test. Immunol. Ser. 1990; 53:13-25.

16. Garner JS and Favero MS. CDC guidelines for handwashing and hospital environmental control,

1985. Infect. Control 1986; 7:231-235.

17. General Hospital and Personal Use Devices Panel, Thirtieth Meeting, Transcript, July 18, 1995.

18. ISO 10993-1:1992 Biological evaluation of medical devices - Part 1: Evaluation and Testing.

19. Kaczmarek, R.G., Moore, R.M., McCrohan, J., Goldman, D.A., Reynolds, C., Caquelin, C., and Israel, E. Multi-state investigation of the actual disinfection/sterilization of endoscopes in health care facilities. Am. J. Med. 1992; 92:257-261.

20. Mandel J. The Statistical Analysis of Experimental Data. John Wiley and Sons, Inc. 1964.

21. Memorandum of Understanding Between the Food and Drug Administration, Public Health Service, Department of Health and Human Services and the Environmental Protection Agency, Notice Regarding Matters of Mutual Responsibility - Regulation of Liquid Chemical Germicides Intended for Use on Medical Devices, June 4, 1993.

22. Interim measures for the registration of antimicrobial products/liquid chemical germicides with medical device use claims under the memorandum of understanding between EPA and FDA. June 30, 1994.

23. Muscarella, L.F. Are all sterilization processes alike? AORN 1998; 67(5):966-976.

24. ODE Blue Book General Program Memorandum #G95-1, May1. 1995. Use of International Standard ISO-10993. Biological Evaluation of Medical Devices Part 1: Evaluation and Testing.

25. ODE Blue Book Memorandum #K97-1 January 10, 1997. Deciding when to submit a 510(k) for a change to an existing device.

26. Official Methods of Analysis of the Association of the Official Analytical Chemists. Ed: Kenneth Helrich, AOAC Inc. Arlington, VA. 1990; Chapter 6:133-146.

27. Rutala WA. Guideline for selection and use of disinfectants. Am. J. Infect. Control 1990 18:99-117.

28. Spaulding EH. The role of chemical disinfection in the prevention of nosocomial infections. In: PS Brachman and TC Eickof (ed), Proceedings of International Conference on Nosocomial Infections, 1970. American Hospital Association, Chicago. 1971:254-274.
29. United States General Accounting Office, Report to the Ranking Minority Member Committee on Government Operations, House of Representatives, Hospital Sterilants: Insufficient FDA Regulation May Pose a Public Health Risk, GAO/HRD-93-79, June 1993.