

**Guidance on the Content and Format of
Premarket Notification [510(k)] Submissions for
Liquid Chemical Sterilants and High Level Disinfectants**

DRAFT

**This guidance document is being distributed for comment
purposes only.**

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Division of Dental, Infection Control
and General Hospital Devices
Office of Device Evaluation
Center for Devices and Radiological Health**

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[Note: Comments should be submitted for agency consideration within 60 days of release of this document on the internet by writing to Chiu S. Lin, Ph.D., CDRH, 9200 Corporate Boulevard, HFZ-480, Rockville, MD 20850 or by e-mail to cxl@cdrh.fda.gov. For questions regarding the use or interpretation of this guidance, also contact Chiu S. Lin, Ph.D. at (301) 443-8913.]

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Devices and Radiological Health

Preface

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).

FDA regulates the introduction of medical devices into interstate commerce. A person intending to market a liquid chemical sterilant or high level disinfectant for use on critical and semicritical medical devices must submit a premarket notification [510(k)] submission to 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). The intent of this guidance document is to provide 510(k) applicants with specific recommendations regarding information and data to be submitted to FDA in a 510(k) submission for liquid chemical sterilants and high level disinfectants.

The effective use of liquid chemical sterilants and high level disinfectants is important in preventing nosocomial infections (Favero and Bond, 1991). The use of comprehensive, scientifically sound criteria for the evaluation of liquid chemical sterilants and high level disinfectants is essential to help ensure that these agents are safe and effective for their intended use. FDA recognizes the importance of providing applicants, and other interested parties, with the agency's 510(k) submission criteria for sterilants and high level disinfectants in order to facilitate assembly of necessary data, to maintain consistency of review, and to provide 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.

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

disinfectants are no longer regulated by the Environmental Protection Agency (EPA). Therefore, FDA finds it necessary at this time to revise its 510(k) submission criteria by implementing FQPA provisions and the agreements between FDA and EPA. This document is a further revision of the October 1995 draft which expresses FDA's recommendations for implementing the provisions of FQPA.

FDA currently is reexamining its germicide evaluation process and has solicited input from industry, users' groups, other regulatory agencies, and academia on FDA's proposed approaches to improving the evaluation of liquid chemical germicides. FDA released a position paper on the internet entitled, "Reexamination of the Evaluation Process for Liquid Chemical Sterilants and High Level Disinfectants," which identifies several of the issues of concern to FDA. FDA's goal is to achieve a more efficient process for bringing liquid chemical sterilants and high level disinfectants to the market while maintaining scientifically sound evaluation criteria. The notice may be found at the following internet address: "<http://www.fda.gov/cdrh/ode/germrp.html>". Although, this document has been revised to reflect implementation of FQPA, the testing criteria recommended by FDA for the evaluation of liquid chemical sterilants and high level disinfectants have not been significantly revised and remain the current FDA recommendations. Revision of this document will commence after receipt of comments on the position paper.

Research and debate with regard to germicide test methods are ongoing. FDA expects that this document and the position paper will stimulate and/or accelerate discussions and the development of germicide test methods and verification procedures by the scientific community and regulated industry. The document is not static and thus, will be revised periodically so that it remains current with state of the art developments in this fast-changing field. Comments on the document are welcome and should be sent to the address noted on [the cover page](#).

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I. INTRODUCTION

A. SCOPE

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

B. EXCLUSIONS

This document does NOT apply to the following:

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 other specific types of devices on a case by case basis;
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 between FDA and Environmental Protection Agency (EPA).

C. DEFINITIONS

1. *Bioburden (microbial load)*: The number and types of viable microorganisms with which an item is contaminated; also known as "bioload" or "microbial load" (AAMI, 1995).
2. *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).
3. *D value (D₁₀)*: Decimal reduction value. The exposure time required under a defined set of conditions to cause a 1-logarithm or 90% reduction in the population of a particular microorganism (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*: According to the Occupational Safety and Health Administration (OSHA), "the use of physical or chemical means to remove, inactivate, or destroy bloodborne pathogens on a surface or item to the point where they are no longer capable of transmitting infectious particles and the surface or item is rendered safe for handling, use, or disposal." [29 CFR 1910.1030] In common usage, "decontamination" generally refers to all pathogens (microorganisms capable of producing disease or infection), not just those transmitted by human blood (AAMI, 1995).
6. *Disinfectant*: A chemical agent that eliminates a defined scope of pathogenic organisms, but not necessarily all microbial forms (e.g., bacterial endospores) (Rutala, 1990).
7. *Disinfection*: The destruction of pathogenic and other kinds of microorganisms by thermal 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, 1972).
10. *Inorganic and Organic Load*: The naturally occurring or artificially placed inorganic (e.g., metal salts) or organic (e.g., proteins) contaminants on a medical device prior to exposure to a microbicidal process.
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 as determined by dose response testing.
13. *Minimum Recommended Concentration (MRC)*: The minimum concentration of a liquid chemical germicide at which efficacy has been demonstrated.
14. *Process Residue*: The substance remaining on a medical device after exposure to a decontamination, disinfection, or terminal sterilization process.
15. *Spaulding Classification*: A strategy for reprocessing contaminated medical devices. The system classifies medical devices as critical, semicritical, or noncritical based upon the risk from contamination on a device to patient safety. The system also establishes three levels of germicidal activity (high, intermediate, and low) for disinfection strategies with the three classes of medical devices (Spaulding, 1970, 1972).
16. *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.
17. *Sterilant*: An agent which destroys all viable forms of microbial life to achieve sterilization.
18. *Sterile*: The state of being free from all living microorganisms; in practice, usually described as a probability function, e.g. as the probability of a surviving microorganism being one in a million (AAMI, 1995).
19. *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).
20. *Sterilization*: A process intended to remove or destroy all viable forms of microbial life, including bacterial spores, to achieve an acceptable sterility assurance level (AAMI, 1995).
21. *Total kill endpoint analysis*: A bracket verification test to confirm the established end point of the germicidal contact time.
22. *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.
23. *Verification*: Confirmation by examination and provision of objective evidence that specified requirements have been fulfilled (Section 820.3 of the FDA Quality System Regulation 1990).
24. *Vegetative State*: An active growth phase of an organism.

D. REGULATORY AUTHORITY AND CLASSIFICATION OF LIQUID CHEMICAL GERMICIDES

FDA regulates medical devices under authority of the Federal Food, Drug, and Cosmetic Act (FD&C Act). Medical devices in commercial distribution prior to

the 1976 amendments to the FD&C Act for medical devices, or the so-called pre-amendments devices, were identified and classified by FDA into one of three regulatory classes: Class I, II, or III. The class established the regulatory controls which are necessary to provide reasonable assurance of the safety and effectiveness of a device. Class I devices are subject to general controls [contact FDA's Division of Small Manufacturers Assistance (DSMA) at 1-800-538-2041 for guidance on general controls]. Class II devices are subject to general controls and any special controls (as amended by the Safe Medical Devices Act of 1990) established by FDA. Class III devices are subject to premarket approval procedures.

In 1980, when the general hospital and personal use devices were classified (45 FR 69678-69737, October 21, 1980), liquid chemical germicides were not included. In subsequent years, FDA actively regulated only liquid chemical sterilants and disinfectants that were used as accessories to specific class II devices, such as hemodialyzers. FDA began actively regulating all liquid chemical germicides in the early 1990s following efficacy testing of the sterilants by FDA for the Environmental Protection Agency (EPA) and publication of the 1993 United States General Accounting Office report on Hospital Sterilants. Since FDA considered them to be accessories to other devices, liquid chemical germicides were regulated 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.

To avoid the confusion that this system would create, FDA determined that liquid chemical germicides were unclassified devices rather than accessory devices. Further, FDA determined that two categories of liquid chemical germicides existed: (1) liquid chemical sterilants which are intended for use as the terminal step in processing critical and semicritical medical devices prior to patient use (semicritical devices contact mucous membranes or nonintact skin during use, while critical devices contact normally sterile tissue or body spaces); and (2) general purpose disinfectants which are intended to process noncritical medical devices (noncritical medical devices make only topical contact with intact skin of the body) and medical equipment surfaces; general purpose disinfectants may also be used to preclean or to decontaminate critical or semicritical medical devices prior to terminal sterilization or high level disinfection. Since the publication of the first draft of this premarket notification guidance document for liquid chemical sterilants and high level disinfectants (germicides) in January of 1992, these devices, though unclassified, have been regulated as class II devices.

Germicides also are regulated by EPA as pesticides under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA). In an effort to resolve the confusion and burden of this dual regulation, on June 4, 1993, a Memorandum of Understanding (MOU) was signed between FDA and EPA giving FDA primary responsibility for premarket review of liquid chemical sterilants and high level disinfectants and EPA primary responsibility for premarket review of general purpose disinfectants. The MOU also provided interim procedures to eliminate dual efficacy data

reviews for the liquid chemical germicides until the rulemaking process to exempt liquid chemical sterilant products from regulation under FIFRA and to classify liquid chemical germicides could be finalized.

In 1996 liquid chemical sterilants used for processing critical and semicritical medical devices were exempted from the definition of a pesticide under FIFRA with passage of the Food Quality Protection Act of 1996 (FQPA) and are no longer regulated by EPA. FDA now has sole regulatory jurisdiction over liquid chemical sterilants and/or high level disinfectants used to process reusable critical and semicritical medical devices. Regulatory authority over general purpose disinfectants was not affected by FQPA. Therefore, the MOU remains in effect for general purpose disinfectants, and the dual regulatory requirements for these germicides continue until the rulemaking process for classification of the germicides is completed.

In an effort to complete the rulemaking process, FDA convened the General Hospital and Personal Use Devices Panel (Panel) in July of 1995 to classify liquid chemical sterilants and general purpose disinfectants. The Panel recommended that liquid chemical sterilants be classified as class II devices (special controls) and that general purpose disinfectants be classified as class I devices (general controls) and be exempted from the premarket notification procedures (section 510(k) of the act).

This guidance document, which is a further revision of the October 1995 draft, pertains only to liquid chemical sterilants and/or high level disinfectants used to process reusable critical and semicritical medical devices. 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 general purpose disinfectants until a Final Rule for classification of all liquid chemical germicides has been published.

E. DEVICE MODIFICATIONS THAT REQUIRE A NEW 510(k) SUBMISSION

21 CFR 807.81 specifies that a premarket notification submission is required when significant modifications are made to the device. Significant modifications to a legally marketed liquid chemical sterilant and/or high level disinfectant which would require a new premarket notification include, but are not limited to, the following examples:

1. a change in the chemical composition of the germicide formulation, such as addition of a new active or inactive ingredient, deletion or substitution of an inactive ingredient, and a change in specifications, such as the concentration of the active or inactive ingredients, the pH, etc.;
2. a change in the indication for use; these changes include, but are not limited to, the following examples:

- a. a change in the lethality claim, such as high level disinfection of endoscopes to sterilization of endoscopes;
 - b. a change in the labeled use conditions, such as addition of a reuse claim or a change in contact conditions (temperature, time, pH, etc.);
 - c. deletion of an exclusion or addition of categories of devices that have restricted design features, such as lumens and mated surfaces, that increase the challenge to the germicide;
3. an extension of the stability expiration date beyond that considered 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.

See also, the document "Deciding when to submit a 510(k) for a change to an existing device," ODE Blue Book Memorandum K97-1, for additional information.

II. GENERAL PRINCIPLES REGARDING PRESENTATION OF DATA

A. EDITORIAL CONSIDERATIONS

The 510(k) submission should be carefully edited and scientifically reviewed before it is submitted to FDA. It should be proofread to assure that all pages are properly indicated, consecutive, distinctly copied, and readable. A well written and organized submission will facilitate the review process.

B. ABBREVIATIONS

Standard abbreviations acceptable to a peer reviewed journal should be used wherever possible. All other abbreviations should be identified at the beginning of each section in which they are used or in footnotes to tables and graphs.

C. DATA AVAILABILITY

This guidance document outlines typical circumstances of data review. It is not possible to anticipate all situations that may require further FDA analyses. Thus, submitters should be aware that they may be asked by FDA to submit additional data, to present data in another format, or to provide more detailed explanations of the information submitted.

Applicants should retain data used for the 510(k) submission in a controlled and well-organized format. This will allow the firm to provide FDA with additional information or analysis, if required. Errors in data that are identified by the applicant after submission to FDA should be brought to FDA's attention immediately.

D. TABLES AND GRAPHS

Well-constructed tables and graphs are fundamental to the reporting and evaluation of data. All tables and graphs should have titles which clearly identify the nature of the data, and all symbols should be captioned and keyed to a footnote or accessible reference page which clearly explains the nature of the symbols.

Graphs should supplement, not replace, data tables. Tables and graphs should be of a quality acceptable to a peer reviewed scientific journal.

E. PUBLISHED LITERATURE

Published methods or data referenced in study reports should be appended to the study report. Reprints of other referenced published reports or data should be appended to the section in which they are referenced. All referenced reports and data should be summarized and an explanation of how this information relates to the current submission should be provided.

F. PROTOCOLS AND DATA ANALYSIS

1. Test reports should include the protocol (objectives, precise description of materials, experimental methods, controls), observations, statistical analyses, conclusions and comments. Additional specific directions on protocols are addressed in other sections of this guidance document.
2. Analytical methods should be clearly described and conform to recognized analytical and statistical methods. For statistical equivalence, please refer to Blackwelder (1982, 1995).
3. Each study report should specify if the study conforms with good laboratory practices regulations, and any deviations should be noted.

G. OTHER CONSIDERATIONS AND COMMENTS

1. The 510(k) should include a response to all elements in Part III below or include an explanation for why data or information has not been supplied, or for why the alternative information provided is sufficient. Original 510(k)s that are grossly incomplete following a cursory review will be immediately deleted with notification to the applicant.
2. A single 510(k) submission will suffice for a common product group, e.g., same active ingredients and claims but different sized containers. Other differences may require submission as separate 510(k)s and will be considered on a case by case basis.
3. Under 21 CFR Section 807.87(h), a 510(k) may be amended to include additional information requested by FDA that is necessary to reach a

finding as to whether the device is substantially equivalent to a legally marketed device. Notification of needed information may be made by telephone and/or in writing. Telephone contact will typically be used to clarify minor deficiencies. Once the applicant is notified of deficiencies, the 510(k) will be placed on hold. Within 30 days of the request for additional information, the applicant should elect to do one of the following:

- a. provide the requested information;
- b. formally withdraw the 510(k) submission;
- c. allow the submission to be withdrawn administratively.

Limited extensions of the 30-day response period may be requested 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 FDA believes a firm cannot respond completely within 30 days, the 510(k) will be immediately deleted with notification to the applicant.

Responses to FDA letters or telephone calls requesting additional information must be submitted in writing to the Document Mail Center. The supplemental information should clearly indicate the assigned 510(k) number and include a restatement of the deficiencies (or append a copy of the deficiency letter) and a complete response. The additional information is considered a supplement to the 510(k). A grossly incomplete response to a request for additional information will not be evaluated and FDA may place the file on hold again after the applicant is notified. A less than comprehensive response may also raise new questions which will need to be addressed. Therefore, in order to minimize review iterations the applicant should respond fully to the request for information.

4. The FDA strongly recommends that nonclinical laboratory studies submitted as part of a 510(k) submission be conducted according to GLP regulations, 21 CFR Part 58. Following GLP regulations will help ensure the quality and integrity of the submitted data.

III. FORMAT AND CONTENT

A. COVER LETTER AND INTRODUCTORY INFORMATION

The guidance document on the preparation of a Premarket Notification 510(k), available from the Division of Small Manufacturers Assistance (DSMA), should

be consulted before beginning work on the 510(k) document. This guidance document for liquid chemical sterilants is a supplement to the 510(k) guidance document. A cover letter clearly indicating, in a subject title, that it is a premarket notification [510(k)] submission, should be submitted with 510(k) submission. The following information should be included 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;
3. the establishment registration number, if applicable, of the owner or operator submitting the 510(k);
4. the FDA product code: **MED** for chemical sterilants and high level disinfectants;
5. the FDA review panel code: INCB;
6. a statement that the germicide is unclassified; according to the panel recommendation, the proposed medical device classification for liquid chemical sterilants and high level disinfectants is class II.
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. identification 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; FDA will discuss the 510(k) only with those individuals designated by the firm as official contacts for the 510(k) submission;
10. the name and address of each facility that will be used for manufacturing, packaging, and storing the germicide and retention of records;

B. TABLE OF CONTENTS

The 510(k) should include a table of contents that notes the section titles and pages. Each section of the document should have its own table of contents.

C. INFORMATION REQUIRED BY THE SAFE MEDICAL DEVICES ACT OF 1990

Under the Safe Medical Device Amendments of 1990, the 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).

Safety and effectiveness information refers to information in the 510(k), including adverse safety and effectiveness information, that is relevant to an assessment of substantial equivalence. The information could be descriptive information or performance or clinical testing information about the new and predicate device(s). A summary shall be in a separate section and be clearly indicated as the 510(k) summary of safety and effectiveness.

Regulations establishing the requirements for the 510(k) summary, the 510(k) statement and the Truthful and Accurate Statement are delineated in 21 CFR 807.92, 807.93, and 807.87(j), respectively. FDA cannot complete the review of the 510(k) submission without the 510(k) summary or statement and the Truthful and Accurate Statement.

In addition, an Indications for Use Statement must be provided in a form recommended by FDA.

Sample copies of the 510(k) and Truthful and Accurate statements and the Indications for Use form may be obtained from the Division of Small Manufacturers Assistance.

D. COMPARISON OF THE NEW GERMICIDE TO THE PREDICATE GERMICIDE

In order to facilitate the finding of equivalence, the submission should 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.

E. OTHER DATA AND INFORMATION

If data and/or information on file with another agency or as device master files are cited, FDA must have access to all of the cited data. As a result, the 510(k) must include authorization from the submitter of the cited data enabling FDA to refer to the information on behalf of the 510(k) applicant.

F. PHYSICAL AND CHEMICAL PROPERTIES

The submission should include complete information on the physical and chemical properties of the germicide.

1. Description of the Germicide

Provide the following information:

- a. a statement of the product formula as it is manufactured, e.g., as provided in the Confidential Statement of Formulation (CSF) as set up by EPA for pesticides (see Appendix A);
- b. the certified limits and nominal concentration for each active and inert ingredient listed in the formula; upper and lower certified limits must be established for each active and inactive ingredient. The upper certified limit is the maximum (and the lower certified limit is the minimum) amount of the ingredient that will be present in the product at any time while it is in commerce;
- 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 molecular, structural, and empirical formulas and the molecular weight for each active ingredient;
- f. the purpose or function of each ingredient;
- g. the source of each of the active and inactive ingredients and the technical information provided by the suppliers of the ingredients;
- h. 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;
- i. the microbicidal mode of action of the final product formulation of the germicide, if known, with references;
- j. a thorough discussion of how the formulation was developed and how the specifications/certified limits were established to ensure that the germicide is safe and effective when used according to labeling; 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; and
 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.

2. Description of the Container

In order to address the effect of the container material on the germicide stability, a complete description of the germicide container(s)/closure(s)

including container sizes, identity of materials, and specifications should be provided. The submission should describe compatible materials for containers that may be used to hold the germicide during in-use sterilization or disinfection of reusable medical devices.

3. Accessory Devices or Containers

Identify any accessory devices or containers specified in the labeling for use with the sterilant or high level disinfectant for heating, aerating, etc. Endoscope reprocessors are addressed in a separate guidance document. (See the document, "Guidance on Premarket Notification [510(k)] Submissions for Automated Endoscope Washers, Washer/Disinfectors, and Disinfectors Intended for Use in Health Care Facilities," for additional information.)

4. Stability Data

Stability data, obtained under the storage conditions and recommended use patterns specified in the labeling, should be submitted to support the following claims, as appropriate:

- a. the expiration date (shelf life) of the unopened marketed stock product(s);
- b. the use period of the opened and/or activated product; and
- c. the reuse life of the product with reusable claims.

NOTE: Since the stability of the microbicidal activity and toxicity of the product are considered under the data requirements for efficacy and toxicity, these data need not be reiterated here.

General Considerations for Stability Testing

Since most liquid chemical sterilants and 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, at 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. The studies should evaluate the chemical composition and physical properties of the germicide, such as color, odor, and clarity, and assess the suitability of the container. The pH and percentage amount of each active and inactive ingredient present in the product and activated solution at each time point should be compared with the initial specifications for the product. The presence and amounts of any impurities initially present or created in the stock or activated product during storage should be assessed. 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 should be addressed.

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

For stability studies supporting the use period of a product after it is opened, unopened containers should be stored under the conditions indicated in the labeling to the expiration date. Following the initial analysis, the opened container should then be stored 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 and then reanalyzed. For example, the storage conditions for products containing multiple use volumes should reflect the repeated opening of the container and removal of solution over the claimed use period. The labeling should emphasize the need for monitoring the concentration of the active ingredient of the germicide preparation before each use and that the decision to use the germicide product must be based on the concentration of the active ingredient and not the days in use.

For stability studies supporting the use period of an activated product with no reuse claim, unopened containers should be stored to the expiration date under the conditions indicated in the labeling. If applicable, the opened container also should then be stored 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. Following analysis of the unactivated product and activated product(s), the activated product should be stored 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 reanalyzed.

For studies supporting the reuse period, unopened containers should be stored to the expiration date under the conditions indicated in the labeling. Following analysis of the unactivated and activated product(s), the activated product should be stressed over the reuse life period using a simulated reuse protocol (e.g., the EPA reuse protocol), stored under conditions indicated in the labeling for the activated product, and then reanalyzed. The labeling should emphasize the need for monitoring the concentration of the active ingredient of the germicide preparation before each use and that the decision to use the germicide product must be based on the concentration of the active ingredient and not the days in use. Reuse life should only be used as the maximum number of days the germicide can be used even if the concentration of the active ingredient is above the minimum effective concentration or the minimum recommended concentration, whichever is applicable, for the germicide.

Stability data should be obtained with each type of container and closure system proposed for marketing. For each type of container and closure system, the largest

and smallest size containers should be included in the study. Compatibility of the product with each container and closure system should be established and the possibility of interaction of leachables from the container with the product during storage should be assessed. Each container and closure system should be evaluated 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.

If a component of a germicide contains a microbiological preservative, then data should be provided on the microbiological preservative content of the product using tests such as the USP Antimicrobial Preservative Effectiveness test or a chemical assay for the preservative. At the minimum, this testing should be conducted at the beginning and end of the shelf life period, the use period, and the reuse life period, as applicable.

Sampling Plan and Times

A sampling plan, including justification of sample size and the method of sampling, should be established. To represent batch-to-batch variability, containers should be randomly selected from at least three different lots for each time point, and each lot should be selected from a different production run. The test samples should represent the lot as a whole. For example, starting at a random point, every nth container should be selected; n is determined by the number of sampling times and the size of the lot. At least two aliquots from each sample container should be analyzed.

Sampling should be sufficiently frequent 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, samples could be analyzed every three months for the first year, every six months for the second year, and then yearly thereafter. If a product is expected to degrade rapidly or if little information is available to support the stability of the product, more frequent sampling will be necessary.

For a new germicide not currently on the market, all available stability data that support the label shelf life should be provided. In lieu of complete stability data supporting the proposed claims, FDA will accept a detailed protocol and sampling plan, as described below, for ongoing stability studies to be continued after clearance. The label shelf life may be amended with the FDA as supporting data are collected. All stability data should be kept on file as part of Good Manufacturing Practices.

The sampling plan, the test protocols, the methods of verification, and the methods of analysis should be described in detail. References to any standards or regulations used as a basis for stability testing should be included. The test report should state the initial, intermediate and final germicide composition and physical properties and other analytical data such as pH. The following additional information should be provided:

- e. the storage conditions (that coincide with labeling);
- f. the identification number and the manufacturing date of each lot;
- g. the size of each lot;
- h. the number of samples selected per lot;
- i. the method used for selecting the samples;
- j. the number of aliquots analyzed per sample;
- k. the method used for taking the aliquots;
- l. the time points for analysis;
- m. the dates of sampling and analysis;
- n. the duration of the study;
- o. calculations and the statistical analysis;
- p. plots and graphs;
- q. any information from previous formulations obtained during product development or in the published scientific literature.

G. LABELING

0. Types of Labeling to Submit

The applicant should submit the following types of labeling in the 510(k):

- a. the label affixed to the germicide immediate container (bottle label);
- b. the package insert;
- c. any other labeling (literature, brochures, pamphlets, and referenced material) provided with or concerning the germicide.

The labeling for the liquid chemical germicide must comply with 21 CFR Section 801.5 and should use terminology currently utilized by infection control practitioners.

The passage of the Food Quality Protection Act of 1996 exempted liquid chemical sterilants used on critical and semicritical devices from the definition of a pesticide under FIFRA. Therefore, these products are no longer regulated by EPA, but are under the sole regulatory authority of FDA. A Pesticide Registration (PR) Notice is to be released by EPA to advise registrants of FIFRA provisions for liquid chemical sterilant products that are intended for use on critical and semicritical devices. The PR Notice should be consulted for additional guidance regarding label modifications stipulated by EPA per FQPA. Liquid chemical sterilants for other use sites and general purpose disinfectants remain EPA-regulated. No EPA references should appear in the labeling for FDA-regulated liquid chemical sterilants.

It is the primary responsibility of reusable device manufacturers to include validated 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 germicide and reusable device labeling should cross-reference one another and thus together provide the user information on how to properly reprocess the device.

The improvement and harmonization of device labeling are actively being pursued by FDA. 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 must be able to stand alone by providing comprehensive information to the user. Notwithstanding the current situation, all germicide labeling should refer the user to the reusable device labeling for additional directions.

1. **Content of Labeling**

The labeling for liquid chemical sterilants must comply with Section 801.5 of 21 CFR and should be consulted for labeling regulations and format before labeling is prepared. FDA recognizes that the health care community must be provided with labeling for germicides that is clear and informative. Therefore, FDA recommends that, in addition to the bottle label that contains only the essential information needed by the user for the safe use of the product, a package insert containing supplemental information also be provided to the user. Please be advised that liquid chemical sterilants and high level disinfectants for use with critical and semi-critical medical devices are no longer regulated by EPA, but are under the sole regulatory authority of FDA. Therefore, the EPA bottle label, previously utilized for liquid chemical sterilant/high level disinfection products, is no longer appropriate.

In addition to the information delineated in 21 CFR Section 801.5, FDA recommends that the bottle label and package insert contain the information described below.

2. **Bottle Label**

The content of the bottle label should include information that is essential to the user. The directions for use and the contact conditions should be clearly stated and easy to read. Terms such as sporicidal, tuberculocidal, fungicidal, bactericidal, and virucidal are EPA-permitted claims and thus should not appear in the labeling for liquid chemical sterilant products. It has long been an FDA policy that, unless proven by clinical trials, there should be no reference to a specific disease, such as AIDS, in advertising, labeling or supporting documents for a device. See Appendix B for a sample bottle label for a high level disinfectant. The following information should be included 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. Indications for Use. Each of claimed level of germicidal activity should be based on supporting potency, simulated use and in use data and should be addressed in the label. Sample statements for each item are provided below:

Germicide Level of Activity (as applicable)

"TRADE NAME is a liquid chemical sterilant intended to sterilize reusable medical devices which contact normally sterile areas of the body when used according to the Directions for Use."

"TRADE NAME is a high level disinfectant intended to disinfect reusable medical devices which contact mucous membranes when used according to the Directions for Use."

"TRADE NAME is a liquid chemical sterilant and high level disinfectant intended to sterilize or disinfect reusable medical devices which contact normally sterile areas of the body and mucous membranes, respectively, when used according to the Directions for Use."

"Sterilant: TRADE NAME is a sterilant when used (state minimum recommended or effective concentration(s), contact time, temperature, etc.)."

"High Level Disinfectant: TRADE NAME is a high level disinfectant when used (state minimum recommended or effective concentration(s), contact time, temperature, etc.)."

Reuse Period (if applicable)

"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. **DO NOT RELY SOLELY ON DAYS IN USE.** Use patterns may reduce the established reuse life of the liquid chemical sterilant."

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.

e. **Warnings**

Note any serious adverse reactions as a result of contact with the germicide and any other potential safety hazards or limitations 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.

g. **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 detailed rinsing and neutralizing instructions, when needed, including the type of rinse and duration and/or volume of rinse to remove residues as determined from testing. The quality of the rinse water, such as pH, presence of dissolved organic material, water hardness, microbial content, and temperature, should be defined in the labeling. Any factors in the rinse water that could interfere with adequate removal of germicide residues from devices should be stated. The instructions may direct the user to the reusable device labeling for any additional instructions specific to the device.
3. State the contraindications. Because liquid chemical germicides cannot be routinely monitored biologically, a statement should be included in the labeling emphasizing that liquid chemical germicides should not be used to sterilize reusable medical devices that are compatible with sterilization processes, such as steam, dry heat, ethylene oxide, or gas plasma, that can be biologically monitored.

h. **Storage Conditions and Expiration Date**

1. State the expiration date of the stock solution.
2. State the storage conditions of the stock solution, activated solution and use-dilutions, as applicable.
3. State the use period for the activated solution and use-dilutions, as applicable. Emphasize that any reuse period is a maximum limit and that the solution must not be used when the concentration of the active ingredient has dropped below the minimum recommended or effective

concentration regardless of the number of days in use. The effectiveness of the germicide is dependent upon the concentration of the active agent(s) remaining at or above the minimum recommended or effective concentration, pH and temperature.

i. **Emergency and Additional Information**

Provide a telephone number for emergencies or for additional information regarding safety and effectiveness of the germicide, such as acceptability of reprocessing devices or materials not listed in the labeling.

j. **Disposal**

State the method for disposal of the germicide and any neutralizers. The directions should be consistent with local and state regulations for disposal of hazardous waste.

3. **Package Insert**

In addition to the information described above for the bottle label, the package insert should contain the following information:

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

The indications for use of a germicide are based upon the "Spaulding classification." The classification scheme for chemical germicides proposed by Spaulding (1970) is incorporated into infection control guidelines of the Centers for Disease Control and Prevention (CDC; Garner and Favero, 1985) and other significant infection control professional organization guidelines. Favero and Bond (1991) and Rutala (1990) have published thorough descriptions of the classification scheme.

The Spaulding classification categorizes medical devices, based upon how the device contacts the patient, as critical (see note), semicritical, and noncritical.

Critical reusable devices must be sterilized between uses. NOTE: The term "critical device" for purposes of this guidance should not be confused with the term as defined under 21 CFR 820.3(f) in the Good Manufacturing Practices regulations.

Semicritical reusable devices should also be sterilized between uses whenever possible, but at a minimum, high level disinfection is acceptable.

Liquid chemical germicide sterilization is acceptable only for those heat sensitive reusable critical devices which are incompatible with all **available methods of sterilization that can be biologically monitored**.

The package insert should contain a brief description of the Spaulding classification scheme. Since liquid chemical sterilants are for use with critical and semicritical devices only, the discussion of the classification scheme should be limited to these types of devices.

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 Compatibility

Note the materials that are compatible and incompatible with the germicide determined from the literature and testing. Refer the user to the labeling of the reusable device for additional instructions.

d. Mode of Action of Germicidal Activity

Describe the microbial mode of action of the final product formulation of the germicide, if known.

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. Precautions

In addition to the information described for the bottle label, provide detailed instructions for cleaning devices in preparation for sterilization or disinfection. The user also should be referred to the reusable device labeling for the manufacturer's recommendations for device decontamination.

g. 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.

h. 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.

H. EFFICACY DATA

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

0. Introduction to Microbiological Qualification Tests

The data and information in a 510(k) must 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 purpose of the qualification tests is to discern similarities and differences, for example, in claims and directions for use, that may impinge upon equivalence. To support sterilization and high level disinfection claims, efficacy data for potency tests, simulated-use tests and in-use tests should be provided as described below.

1. Study Report Content

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

- 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:
 - 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; and
 14. all controls.
- c. detailed results, thoroughly analyzed, with graphs and tables; and
 - d. conclusions which summarize the findings that are supported by the test results.

Each test method should be demonstrated to be reproducible or it should be a reference standard test. All variances from reference tests should be explained. The protocol should provide for sufficient samples and replicates to ensure statistical significance at the 5% level with statistical power of at least 90%. The analysis of data should be thorough and include statistical evaluations whenever possible, e.g., survival data analysis.

2. Potency Tests

Potency tests are used to compare sterilants and to evaluate substantial equivalence of the subject sterilant with a legally marketed sterilant. These tests demonstrate the potential use of the sterilant for sterilization or high level disinfection of medical devices. All potency testing should demonstrate the performance of the sterilant under worst case conditions and when exposed to organic and inorganic challenges as described below:

- a. Microbiological tests run by the applicant that are not standard reference tests, should demonstrate the performance of the germicide when exposed to an organic and inorganic challenge. The challenge should be at least as rigorous as recommended in the Association of Official Analytical Chemists (AOAC) methods and EPA methods.
- b. Microbiological tests should validate the effectiveness of the germicide under worst case conditions, including temperature extremes, and other factors as appropriate, such as light, which may affect the efficacy of the germicide.

Ideally, worst case conditions for a single use germicide would be a germicide from a production run, stored to expiration and at its minimum specifications (diluted, if necessary).

Ideally, worst case conditions for a reused germicide would be 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. The simulated reuse protocol should incorporate any factors that may impact the performance of the germicide, such as an organic load, dilution, water quality, temperature variation, pH changes, etc.

NOTE: The EPA Re-use Test Protocol is an example of a simulated reuse protocol.

- c. The microbial test organisms identified in this section are selected to establish a broad spectrum of microbicidal activity. Additional relevant test organisms may be required for germicides that are indicated for specific types of devices and conditions of use, e.g., dialyzers.

3. **Sterilization Claim**

Sterilization is defined as a process intended to remove or destroy all viable forms of microbial life, including bacterial spores. Since the absence of all forms of life cannot be proven unequivocally, the use of a sterility assurance level (SAL) has become an accepted endpoint for establishing sterility. An SAL is the probability of survival of microorganisms after a terminal sterilization process and is based on the evaluation of survivor curves that exhibit a kinetics model that can be mathematically derived. The SAL for devices entering normally sterile areas of the body has been defined by FDA as 10^{-6} . This means that the probability of contamination is one device out of one million devices processed.

For example, a probability of microorganism survival of 10^{-6} means that if each unit of product was contaminated with one microorganism (10^0), the

process could inactivate an additional six logarithms of microorganisms. In other words, there is less than or equal to one chance in a million that a particular item is contaminated or nonsterile. It is generally accepted that a sterility assurance level of 10^{-6} is appropriate for items intended to come into contact with compromised tissue (i.e., tissue that has lost the integrity of the natural body barriers). A sterility assurance level of 10^{-3} (a one in a thousand chance of a surviving microorganism) is considered acceptable for items not intended to come into contact with compromised tissue.

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 have been studied relatively less extensively. The studies that are available in the literature suggest that sterilization processes based on liquid chemical sterilants, in general, may not convey the same sterility assurance as sterilization achieved using thermal or physical methods. 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 and chemical nature of the liquid chemical germicide. In addition, the AOAC Sporicidal Test does not confirm an SAL of more than 10^{-2} . Therefore, sterilization with a liquid chemical sterilant may not convey the same sterility assurance as that of other sterilization methods, such as steam sterilization.

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. 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.

Recommended conditions for device sterilization may be established as described below; however, based on the above limitations, FDA recommends that liquid chemical sterilants be used only for reprocessing heat-labile devices that are not compatible with other sterilization methods that can be biologically monitored, unless otherwise indicated in FDA-approved labeling.

To support a device sterilization claim, the following information should be provided:

- a. A study report should be submitted showing that a germicide formulation claimed as a sterilant passes the AOAC Sporicidal Test as a sterilant, i.e., no failures, under the worst case conditions of germicide composition (as defined in Section 3b) when used according to labeling. Three lots, preferably from different production runs, should be tested according to the AOAC Sporicidal Test method. Confirmatory testing should be conducted using two of the three lots.

As a sterilant, a germicide should pass the test within 20 hours of contact and should be comparable to the sterilization contact time for the claimed predicate germicide. Material compatibility concerns and the lack of information in the published scientific literature about the sporicidal mode of action of liquid chemical sterilants on spores compel FDA to limit the contact time necessary to achieve sterilization to 20 hours or less, at this time.

Presently, FDA will not accept the results of AOAC Sporicidal Tests with any substitutions for the carriers. FDA is aware of the concerns about possible interactions between the silk sutures and some germicides and we are investigating the issue. We will publish any recommendations resulting from the findings of the investigation.

- b. The study report should provide information on how the contact time was determined. The precise total kill contact time should be validated by end point analysis. Note that these data may be generated during conduct of the AOAC Sporicidal Test, but the organism/carrier pair which presents the greatest challenge to the germicide should be used. The verification data will show whether there are spore survivors beyond the total kill time, i.e., it will further verify sterilization. The test should evaluate performance under the worst case conditions for the germicide.

The end point analysis should include multiple points on either side of the total kill point. FDA recommends that the analysis include time points at 15 minute intervals at least one hour before and one hour after the total kill contact time. As an example of end point analysis, inoculated sample tubes, in groups of 60, are each neutralized at time points before and after the established total kill point. Some groups before the total kill point should include tubes with growth and no groups after the total kill point should show growth. The number of samples and replicates should be sufficient to ensure confidence in the results, if statistical testing methods are not to be used.

- c. In order to support a sterilization claim, the biological lethality profile of the germicide should be determined. The proposed sterilant must also pass the following additional tests at the test conditions defined in the method noted:
 1. Quantitative Tuberculocidal Test or AOAC Tuberculocidal Test;
 2. AOAC Fungicidal Test;
 3. AOAC Use-Dilution Tests for *S. aureus*, *S. choleraesuis*, and *P. aeruginosa*; and
 4. Virucidal Test previously recommended by EPA for its germicide registration program.

4. **High Level Disinfection Claim**

- a. In order to support a high level disinfection claim, the germicide must pass the AOAC Sporicidal Test as a sterilant as indicated under the Sterilization Claim above.
- b. A study report should be submitted showing that the contact time for high level disinfection is sufficient to achieve a 6 log reduction of *Mycobacterium tuberculosis* var. *bovis* under worst case conditions (as defined in Section 3b) of germicide composition. An alternative representative mycobacterium species may be used if it can be demonstrated with test data or literature references that the resistance of the organism to the chemical is similar to *Mycobacterium tuberculosis* var. *bovis*. Testing may be conducted with the mycobacterium in suspension or on carriers, but the number of organisms on the carriers must be quantitated. Control carriers must be run concurrently with the test group.
- c. In order to support a high level disinfection claim, the biological lethality profile of the germicide should be determined. The proposed high level disinfectant must also pass the following additional tests at the test conditions defined in the method noted:
 1. AOAC Fungicidal Test;
 2. AOAC Use-Dilution Tests for *S. aureus*, *S. choleraesuis*, and *P. aeruginosa*; and
 3. Virucidal Tests previously recommended by EPA for its germicide registration program.

5. **Simulated-Use and In-Use Tests**

a. **Introduction**

A chemical germicide is effective only when it comes in contact with the contaminated surfaces and when the required contact conditions of time, pH, temperature, and any other critical variables are met. Simulated-use tests help to further determine the penetrating capability of the germicide and other factors that prevent or limit contact and effectiveness, i.e., the tests help identify conditions under which the germicide will fail. Simulated-use tests are controlled tests which allow the **precise application of a specified and quantified inoculum to selected device**

surfaces. Simulated-use tests are also required under the good manufacturing practices regulation, 21 CFR Part 820.

Since simulated-use studies on the performance of medical devices cannot anticipate all outcomes during clinical use, in-use testing is needed to confirm the results of simulated-use testing. FDA believes that the persistence and resistance of ambient bioburden, such as biofilms including wild microbial strains and other unforeseen factors, may limit adequate correlation of simulated- and in-use testing of the germicide.

All available and relevant simulated- or in-use performance data, both positive and negative, should be reported. These data may include studies conducted by the applicant, data published in the scientific literature, and studies by reusable medical device manufacturers. The applicant should summarize the data and justify how the data support a finding of substantial equivalence. The data should include evaluation of the germicide under worst case conditions for germicide composition (see Section 3b).

The applicant should 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. Tests conducted with the predicate device are not needed unless special circumstances require additional testing. All failures should be documented and analyzed for causation. The findings of the simulated-use and in-use tests should be reflected in the labeling, e.g., limitations on use, adjustments to conditions of use, precautions, etc.

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 are unnecessary. In this case, germicide labeling can refer the user to the reusable device labeling for more specific instructions. The 510(k) should include labeling from these reusable devices in order to confirm that the reusable device 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). The applicant should refer to the June 1996 draft guidance document, "Labeling Reusable Medical Devices for Reprocessing in Health Care Facilities" for further instruction.

b. General Considerations of Testing

The test battery for simulated- and in-use studies should consist of the following elements:

1. The tests should 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. The tests should incorporate devices with the type of materials indicated in labeling as compatible.
 3. Replicate devices should be tested to obtain reliable results. The number of samples and replicates should be sufficient to ensure confidence in the results, if statistical testing methods are not to be used. A rationale should be submitted for the number and type of reusable devices selected.
 4. A description of the microorganism recovery method and each method used to verify the recovery method should be provided. The verification should identify the minimum number of organisms that can be detected by the recovery method. In addition, the firm should 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). In addition, the verification should demonstrate that the incubation period is adequate to allow for growth and that the neutralization method has no germicidal effect and does not otherwise interfere with the microbicidal activity of the germicide. Ideally, the same lot of media should be used throughout testing. If a new lot of media is introduced, then the test method should be reverified. The ability to recover at least 90% of the injured organisms with the media should be demonstrated.
 5. Test reports indicating the compatibility of the germicide with any cleaning and defoaming agents indicated in labeling should be submitted.
 6. All tests should include appropriate controls.
- c. **Simulated-use Testing**

Sterilization claim: The test organism should be a spore at an inoculum of at least 10^6 cfu/ml. FDA expectations are no survivors with a 6 log challenge. However, all failures should be documented and analyzed for causation.

High level disinfection claim: The test organism should be the most resistant mycobacterium species at an inoculum of at least 10^6 cfu/ml. FDA expectations are no survivors with a 6 log challenge. However, all failures should be documented and analyzed for causation.

The following additional elements should be considered when planning and conducting simulated-use testing:

1. The devices selected for testing should represent critical or semicritical devices depending on the intended use of the germicide. For example, a high level disinfectant should be tested on semicritical devices. If the labeling indicates use of the sterilant with only certain specific devices, then those devices should be tested.
2. The tests should incorporate other factors that impede cleaning and germicide activity, e.g., a representative inorganic and organic challenge added to the inoculum. The organic challenge should be representative of the type of organic load to which the device is exposed during actual use such as serum, blood, secretions, etc. Although 5% BSA and hard water are commonly referenced as examples of organic and inorganic challenges, respectively, justification for their use in simulated-use testing should be provided. FDA may be consulted for advice about what type of challenge to use in simulated use testing.
3. The microbial challenge and the method of inoculation of devices in simulated-use tests should be described in detail. The most difficult areas for the germicide to penetrate and contact should be inoculated and the inoculated device should be allowed to dry. The inoculum on the device and the wash-off factor should be quantified to determine the challenge to the germicide.
4. The germicide solution should be stressed, aged and at its MRC or MEC. Following exposure to the solution for the sterilization or high level disinfection contact time noted in the labeling, the test device should be removed and rinsed, brushed and then rinsed again according to the verified organism recovery method. All rinses and brushes should be cultured with growth media shown to support growth of low numbers of organisms.

d. In-use Testing

In-use testing should be conducted in a clinical setting using multiple devices and in conjunction with the facility personnel who have been instructed to clean, reprocess and rinse the test devices according to label instructions. In addition to the elements listed under General Considerations of Testing above, in-use reusable device test samples should be precleaned according to the reusable device labeling when it is more specific. No extraordinary methods of preparation of the device prior to exposure of the device to the germicide should be employed. The germicide solution should be freshly prepared as described in the labeling. The microbial

challenge should be quantitated before and after cleaning a representative control device.

Product with a sterilization claim alone: In-use testing should be conducted according to the label contact conditions for device sterilization. FDA expectations are no surviving organisms. If failures occur, the manufacturer should document and analyze each failure for causation, and then reevaluate the proposed label contact conditions for the sterilization claim.

Product with a high level disinfection claim alone: In-use testing should be conducted according to the label contact conditions for high level disinfection of devices. If failures occur, the manufacturer should document and analyze each failure for causation, and then reevaluate the proposed label contact conditions for the high level disinfection claim.

Product with both sterilization and high level disinfection claims: In-use testing should be conducted according to the label contact conditions for high level disinfection. FDA expectations are no surviving organisms. If no failures occur, then in-use testing at the longer contact time for sterilization may be waived. If failures occur, the manufacturer should document and analyze each failure for causation, and then reevaluate the proposed label contact conditions for both the sterilization and high level disinfection claims.

If the processed reusable devices are retreated with a legally marketed sterilizer or germicide, whichever is appropriate, before being returned to service, then testing of germicides in health care facilities can be considered minimal risk studies under 21 CFR Part 56, which do not require prior FDA approval under Investigational Device Exemption (IDE).

6. Other Tests

As appropriate for each germicide product, additional testing should be conducted to evaluate those factors not addressed above but that may influence the microbicidal effectiveness of the germicide.

7. Summary of Microbiological Test Data

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

I. **BIOCOMPATIBILITY**

0. **Introduction**

Germicide residues that remain associated with devices following reprocessing may pose a risk to patients and users. The residue may be the germicidal active ingredient, 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 the amount of residue prior to reuse. Therefore, it is important that the residues that remain associated with devices following reprocessing and rinsing be analyzed and quantified and that the potential health risks that these residues pose to patients and users be 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 also should be assessed.

1. **Residue Data**

As with simulated- and in-use testing noted in Section H above, labeling for certain reusable devices may include verified instructions for reducing germicide residues on the device to a safe level. The germicide labeling should refer the user to additional instructions in the reusable device labeling.

Since not all reusable devices include verified procedures for reducing residues to a safe level, the 510(k) submission for the germicide should include comprehensive data regarding residues. Representative devices should be exposed to the germicide at the maximum specified use concentration for the maximum contact time required in the labeling before the items are rinsed. Following the residue reduction step (rinsing) as described in the labeling, an initial exhaustive extraction of residues from the whole device should be conducted at 37°C using an appropriate solvent, such as deionized water or normal saline. Approximately 24 hours following the completion of the initial extraction, a second extraction should be conducted using the same solvent, but for a shorter period of time, e.g., 4 hours.

Although a patient may be exposed to a device for only 15-20 minutes, no information currently is available that describes the rate at which residues may be released from the device. Therefore, we have taken a conservative approach and assumed that all residues remaining associated with a device are potentially available to the patient or user during exposure. Therefore, we recommend exhaustive extraction of residues from the entire device.

The type and amount of residue remaining should be evaluated according to the toxicological evaluation discussed below. The residues of all germicide ingredients, both active and inert, should be quantified and evaluated or justification should be provided for why analysis is not necessary.

The list of test materials does not need to be exhaustive, but should include representative devices with component materials indicated in the labeling as compatible with the germicide. The scope of devices tested should 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. The germicide labeling may refer primarily to compatible materials which may make the residue test scheme simpler. In this case, simulated material test articles may be used to evaluate residue retention and reduction on devices. Alternatively, these data may be replaced or supplemented with studies in the published scientific literature on material retention of the germicide residues.

The labeling (as noted in Section G) should be based upon these data. The residue reduction step (e.g., rinsing) should be detailed and sufficient for all labeled germicide use conditions and must not recontaminate the processed reusable device.

2. Evaluation of Toxicity

To ensure the safe use of the germicide product and of germicide-treated devices, the toxicity of the germicide solution and of all residues remaining on a reusable medical device following reprocessing with a germicide should be assessed. This information will assist FDA in the evaluation of the potential health risks to patients and users from germicide residues remaining associated with the device and to users handling the germicide solution.

During evaluation of residues, both the active and inert ingredients should be considered. The residues that are of concern should be identified and justification should be provided for excluding any residues. Evidence then should be provided showing that the amount of each residue of concern remaining on a device is at a safe level.

The toxicological evaluation of the germicide solution and the residues may be accomplished by reviewing the available toxicity data of the germicide solution and of the identified residual chemicals from animal toxicity studies sponsored by the manufacturers of the active and inert ingredients and in the published scientific literature. Copies of all references should be provided. If adequate information is not available from manufacturers or the published literature, then toxicity testing will be

needed for the individual ingredients of the germicide product and for the germicide product itself at its maximum specified use concentration.

The types of toxicity data required to evaluate the residues will depend on the type of contact the reusable device makes with the body, and the expected duration and frequency of patient contact with the processed reusable device. To address the toxicity of the residues, in general, the following tests using the germicide product and/or the individual ingredients are noted:

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

Multiple dose levels of residue components should be used to construct a dose-response curve to which the actual residue level can be compared. If the data from the above tests show that the use concentration is not toxic, then one can assume that the residues that remain associated with the device are at a safe, nontoxic level.

The above tests, excluding cytotoxicity and hemocompatibility/hemolysis tests, also will be used to evaluate the toxicity of the germicide product and potential health risks to the user due to handling of the germicide solution. The following additional tests are suggested:

- 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. Testing should be conducted with the germicide product at its maximum specified use concentration.

The applicant should refer to the ISO 10993-1 and 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. The applicant should provide a complete description of the toxicity test methods and cite, in each study report, any guidelines and methods used for conducting the tests.

K. DEVICE AND MATERIAL COMPATIBILITY QUALIFICATION

0. 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 will make the device more difficult to clean and may cause injury during use. In addition, clouding of the lens of an endoscope will decrease visibility and thus the effectiveness of the device. For these reasons, the 510(k) for the liquid chemical sterilant products should 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.

The applicant may submit any relevant data to support compatibility claims. These data requirements may be satisfied by reviewing the published literature or information from the manufacturers of the devices and/or component materials showing the compatibility of the germicide with the claimed devices/materials or general device and material classes. If the available data from these sources are inadequate, then compatibility testing should be conducted to support the germicide labeling claims according to the testing discussed below.

The information and/or test data that should be provided will depend on the claims that are made in the labeling 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. Each claim must be supported by compatibility data from the published literature, from the device and material manufacturer, or obtained through testing.

For any specific reusable device claims, the germicide labeling cannot supersede the reusable device labeling. For example, if the labeling for the reusable device recommends a specific type of sterilization or disinfection process, the germicide labeling may not include the specific device as a compatible device, even though testing by the germicide 510(k) applicant may qualify a germicide for reprocessing the particular reusable device. However, the germicide applicant may communicate with the manufacturer of the reusable device to seek modification of the labeling for the reusable device.

1. Testing for Device/Material Compatibility

Devices and materials to be tested: The type of devices and materials that should be tested depends on the claims made in the germicide and reusable device labeling. If labeling for a reusable device indicates compatibility with the germicide, then redundant testing on that device is not necessary. The labeling for the germicide can refer the user to the labeling for the reusable device. The user can also be directed to contact the germicide or device manufacturer for further information.

If the labeling for the germicide indicates compatibility with specific materials, then each material should be tested. When germicide labeling indicates compatibility with a class of test articles (devices and/or materials), the applicant should select test articles that are representative of the class and justify the selection. Even after a finding of substantial equivalence, the applicant should continue with a program of product testing to analyze compatibility of the germicide with other devices and materials in classes studied but not comprehensively evaluated. These data may lead to labeling modifications or can be used as a resource for users of the germicide.

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.

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, e.g., use requirements.

Assessment of the process life of the devices and materials for compatibility with the germicide is described below. An acceptable process life should be defined for each device and material and justification should be provided. 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, the applicant may submit justification for the projected compatibility of the test article based upon extrapolations.

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

Reusable device analysis: The submission should characterize the effect of repeated processing on the functionality of replicate test devices. Functionality testing on materials alone is conceivable, but verification data showing that the test correlates to actual device use should be submitted. 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. The test should incorporate simulated-use conditions on the test articles between processes. Since the germicide manufacturer is not necessarily knowledgeable on the proper functioning of the reusable device and does not have access to the specifications for the device and its component materials, the germicide 510(k) applicant should consult the reusable device manufacturer for collaborative compatibility testing of the device. Evidence of material degradation which is characteristic of each material should be analyzed by visual examination. For example, metals should be examined for discoloration, corrosion, cracking, crazing, and embrittlement.

Extensive published test methods for each parameter noted are available and the applicant should refer to the literature when devising test protocols. The method of preparation of test devices/materials and methods and criteria for analysis of each parameter should be described in the report.

L. CHEMICAL INDICATORS FOR LIQUID CHEMICAL GERMICIDES

Germicides 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 ingredients in the germicide solution. Germicides which require an indicator, and for which there is not a legally marketed indicator available, will not be found equivalent. A chemical indicator for a germicide that is marketed separately from the germicide will require the submission of a separate 510(k).

0. Description of the Chemical Indicator System

The submission should include complete information on the physical and chemical properties of the chemical indicator. Provide the following information:

- . the formulation of the indicator system, including the name of each reactive and nonreactive component and the quantity, proportion or concentration of each reactive ingredient;
- a. the purpose or function of each component;
- b. the chemical principle of the test system, include a diagram of the reaction;
- c. substances that interfere with the efficacy of the test system.
- d. a complete description of the packaging; and
- e. a summary and explanation of the test, including the clinical utility, indications for use and significance of the test.

1. Labeling for Chemical Indicators

Provide the following information in the package insert:

- . Intended Use - Identify the analyte or test objective and type of procedure, i.e., qualitative, semi-quantitative or quantitative;
- a. Summary and Explanation of the Test - Include clinical utility, indications for use and significance of the test;
- b. Chemical Principle of the Test Procedure - Include a diagram of the reaction;
- c. Storage and Stability (as applicable):
 1. Indicate any limits on exposure to light, heat, moisture, strong acids, bases, heavy metals, etc.;
 2. State the correct storage temperature when the reagent is opened and provide storage conditions before opening, and caution user about variation in storage conditions;
 3. State expiration dates of the unopened and opened container;
 4. Provide a space on container for recording date opened; and
 5. Provide visible indications for reagent instability.
- d. Specimen Collection and Preparation;
- e. Assay Procedure - Include amount of sample required;
- f. Materials Required - Identify materials provided and materials not provided;
- g. Quality Control Procedures -
 1. Identify commercially available products that should be used for positive and negative controls, if materials are not provided in the kit;
 2. Indicate frequency and levels of quality control;
 3. Provide directions for interpretation of results of QC material (satisfactory limits of performance);
 4. Indicate the storage conditions for the unopened and opened indicator.
- h. 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 direct comparison with a color chart;

- i. Limitations -
 1. Identify interfering substances; and
 2. State a caution for users who are color blind, when appropriate;
 - j. Performance Characteristics - Provide the results of the comparison testing as described in part 4 below;
 - k. Warnings and Precautions -
 1. Identify potential safety hazards, e.g., "Warning, Toxic Strips. Contain the following chemicals:..." and cautions regarding ingestion, eye exposure, etc.;
 2. Include 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;
1. Selected Bibliography.

2. Performance Testing

Performance testing data should be provided to support the labeling claim that the chemical indicator can accurately and reproducibly measure the MEC or MRC of the liquid chemical sterilant.

Testing of the chemical indicator should address the following items:

- . Provide 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.
 - a. Provide a description of the color development for the periods of time less than and longer than the time period specified for reading the results. Otherwise, provide justification as to why a description at such time points is not necessary.
 - b. Provide the protocol for determining the shelf lives (expiration date) of the unopened and opened containers at required environmental conditions.
- ### 3. General Considerations for Performance Testing
- . Replicate indicators should be tested to obtain reliable results. The number of samples and replicates should be sufficient to ensure confidence in the results. A rationale should be submitted for the number and type of indicators selected. 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.

- a. The results of comparison testing should be analyzed 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);
 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);
 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).

- b. The specifications for the test should be such that the accuracy of a "Pass" or color indication of sufficient active ingredient falls entirely within the effective range of the active ingredient.
- c. Testing should demonstrate the performance of the test system in the presence possible germicide solution contaminants, such as detergents and organic and inorganic material. For example, the testing could be conducted using the worst case germicide composition as described on pages 26-27 under Section 3b of Efficacy Data.
- d. Actual use testing should be conducted for color and/or hue change analysis using test readers, as applicable.

IV. CONTACTS AND ADDRESSES

General questions regarding the submission of premarket notifications should be directed to the Division of Small Manufacturers Assistance at (800) 638-2041 or (301) 443-6597.

Questions regarding this guidance document should be directed 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 _____ Sterilization _____ High level disinfection
 12. _____ Simulated-use Test Data _____ Sterilization _____ High level disinfection
 13. _____ In-use Test Data _____ Sterilization _____ High level disinfection
 14. _____ Residue Data
 15. _____ Toxicity Data
 16. _____ Material/Device Compatibility Data
 17. _____ Chemical Indicator Labeling
 18. _____ Chemical Indicator Performance Data
-

VI. APPENDIX A

Attached is a sample EPA Confidential Statement of Formula.

VII. APPENDIX B
SAMPLE BOTTLE LABEL
KILLCIDE DISINFECTANT SOLUTION
One Gallon
Glutaraldehyde.....10%
Inert ingredients.....90%
Total.....100%

Killcide, Inc.
Anywhere, USA

INTENDED USE: KILLCIDE is intended for high level disinfection of medical devices by immersion for 20 minutes at 20C.

KILLCIDE is a high level disinfectant when used according to the Directions for Use at 20C and at a minimum recommended concentration of 10% glutaraldehyde with an immersion time of at least 20 minutes.

KILLCIDE can be reused for up to 7 days provided the required conditions of concentration of glutaraldehyde (10%), time (20 minutes) and temperature (20C) exist based on monitoring with ARTEST Indicator Strips, a timer and a thermometer.

WARNING: Harmful if swallowed. Contact emergency personnel immediately if swallowed.

PRECAUTIONS: Use personal protective equipment during use of this product.

DIRECTIONS FOR USE:

Preparation of solution: Empty 1 gallon bottle of KILLCIDE into a plastic container. The product should NOT be diluted.

Preparation of devices: Thoroughly clean devices to be disinfected according to device manufacturers instruction.

Disinfection: Immerse device in KILLCIDE solution and fill any device channels with solution, being careful to remove all air from any device channels. The device should remain in contact with KILLCIDE solution at 20C for at least 20 minutes. Remove device from the solution, drain the channels and rinse according to the following directions.

Rinsing: All nonsterile water used for rinsing should be filtered through a 0.2 filter. Immerse device in 3 separate 1 gallon volumes of water for 1 minute while flushing all channels. Use fresh water with each rinse. See the device manufacturer's instructions for additional information about rinsing the devices.

Reuse: KILLCIDE may be reused for a maximum of 7 days provided the minimum recommended concentration of 10% glutaraldehyde, time and temperature are maintained. ARTEST Indicator Strips should be used before each use of KILLCIDE solution to determine whether glutaraldehyde is at its minimum recommended concentration of 10%.

DO NOT RELY SOLELY ON DAYS IN USE. Use patterns may reduce the established reuse life of KILLCIDE. Discard if the concentration of glutaraldehyde in the KILLCIDE solution falls below the minimum recommended concentration of 10% glutaraldehyde.

DO NOT USE BEYOND 7 DAYS EVEN IF THE CONCENTRATION OF GLUTARALDEHYDE IS ABOVE THE MINIMUM RECOMMENDED CONCENTRATION (10%) AS INDICATED BY THE ARTEST INDICATOR STRIP.

KILLCIDE is effective as a high level disinfectant only if devices are cleaned thoroughly, the solution is at or above the minimum recommended concentration of 10% glutaraldehyde and the solution is used according to the Directions for Use.

Storage: Store unused solution at 15-30C away from sunlight.

Store reusable solution at 15-30C in a plastic container away from sunlight.

The **expiration date** for KILLCIDE Disinfectant solution is 3 years from the date of manufacture: **1/1/98**.

For emergencies or additional information regarding safety and effectiveness of KILLCIDE, contact Killcide, Inc. at 000-000-0000.

Disposal: To discard KILLCIDE Disinfectant solution safely, first neutralize the glutaraldehyde by adding one vial of KILLCIDE Neutralizing Solution and mix well. Flush the neutralized solution down the drain with water.

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(Updated January 12, 1998)