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Technical Information Report

AAMI TIR7:1999

Chemical sterilants and high level disinfectants: A guide to selection and use

AAMI Association for the Advancement of Medical Instrumentation

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AAMI TIR No. 7:1999
(Revision of AAMI TIR No. 7:1990)

Chemical sterilants and high-level disinfectants: A guide to selection and use

Approved 18 October 1999

Abstract: This Technical Information Report (TIR) covers the selection and use of chemical sterilizing agents (except for ethylene oxide) that have been cleared for marketing by the Food and Drug Administration (FDA). Topics specifically addressed include the general safety and performance characteristics of chemical sterilants and high-level disinfectants; the basic types of chemical sterilants/high-level disinfectants and chemical sterilization techniques; the mechanisms by which manufacturers obtain FDA clearance for the marketing of their products; and questions that users should ask of manufacturers when choosing a product for use on a particular medical device. The TIR also provides general guidance on the use of chemical sterilants and high-level disinfectants, as well as a glossary, a bibliography, and informative annexes.

Keywords: formaldehyde, gas plasma, glutaraldehyde, high-level disinfection, hydrogen peroxide, liquid chemical sterilants, materials compatibility, peracetic acid

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AAMI Technical Information Report

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Association for the Advancement of Medical Instrumentation

Sterilization Standards Committee

This Technical Information Report was balloted and developed by the Chemical Sterilants Hospital Practices Working Group under the auspices of the AAMI Sterilization Standards Committee. Committee approval of the Technical Information Report does not necessarily imply that all working group members voted for its approval.

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NOTE—Participation by federal agency representatives in the development of this Technical Information Report does not constitute endorsement by the federal government or any of its agencies.

AAMI Technical Information Report AAMI TIR No. 7:1999

Chemical sterilants and high-level disinfectants: A guide to selection and use

1 Introduction and scope

1.1 General

This Technical Information Report (TIR) is intended to assist health care personnel in the selection and use of legally marketed liquid chemical sterilants/high-level disinfectants (HLDs) and gaseous chemical sterilization methods. This report is also meant to serve as a resource that health care personnel can use when directing questions to manufacturers about the suitability, effectiveness, and toxicity of specific products.

1.2 Scope

This TIR covers sterilizing agents that have been cleared for marketing by the Food and Drug Administration (FDA).[1] The Food Quality Protection Act (FQPA) of 1996 ended Environmental Protection Agency (EPA) registration of liquid chemical sterilants/HLDs intended for use on reusable critical and semicritical medical devices. Before passage of the FQPA, liquid chemical sterilants/HLDs intended for use with critical and semicritical medical devices were required to be registered by EPA and cleared by FDA before marketing. (For further information, see 5.)

The scope of this report includes

a) the general performance and safety characteristics of liquid chemical sterilants/HLDs and gaseous chemical sterilants;

b) the basic types of liquid chemical sterilants/HLDs and gaseous chemical sterilants;

c) the mechanisms by which manufacturers obtain FDA clearance for marketing their products;

d) the questions that users should consider when choosing a product for use on a particular medical device;

e) general guidance on the use of liquid chemical sterilants/HLDs and chemical sterilization techniques;

f) a glossary, bibliography, and informative annexes.

Many of the liquid chemical sterilants described here are used primarily as high-level disinfectants. Liquid chemicals classified or labeled only as general-purpose disinfectants are excluded from the scope of this report. The classification of the germicidal activity of chemical disinfectants and recommendations concerning their use are covered in the 1985 guidelines issued by the Centers for Disease Control (CDC, 1985). In addition, the Association for Professionals in Infection Control and Epidemiology (APIC) has developed guidelines for the selection and use of disinfectants (Rutala, 1996). Disinfection is also addressed in AAMI (1996b).

Also excluded from this report are sterilizing chemical agents and formulations that have not been cleared by FDA. Finally, this report does not address ethylene oxide (EO) sterilant formulations and sterilization techniques, which are covered extensively in AAMI (1999a), AAMI (1999b), and Danielson (1998).

1.3 Need for the TIR

Basic, user-oriented technical information is needed to help health care personnel understand the action, advantages, and limitations of each liquid chemical sterilant/HLD and chemical sterilization method so that they can

[1] For information on sterilants and HLDs cleared by FDA, contact either the Chief, Infection Control Devices Branch (HFZ-480), Center for Devices and Radiological Health, FDA, 9200 Corporate Blvd., Rockville, MD 20850 (301/443-8913); or FDA's Web site at http://www.fda.gov/cdrh/ode/germlab.html. The list provided at FDA's Web site identifies the liquid chemical sterilants and HLDs cleared by FDA in a 510(k) with general claims for processing reusable medical and dental devices. It does not include preamendment products, FDA-cleared germicides dedicated to specific devices such as hemodialyzers or hemodialyzer machines, or gaseous chemical sterilization systems.

(a) select the agent/method best suited for the intended task (i.e., the processing of a critical or semicritical device), (b) use it effectively, and (c) be aware of potential adverse health effects.

Several concerns have heightened attention to the safety and efficacy of germicides in general and of liquid chemical sterilants/HLDs in particular. First, materials compatibility concerns have arisen from the increase in the variety and concentration of active ingredients in liquid chemical sterilants/HLDs and from the proliferation of new types of plastics for use in the construction of medical devices and chemical sterilant containers. Second, environmental and occupational exposure issues are associated with liquid chemical sterilant/HLD formulations and chemical sterilization systems.

Finally, emerging new diseases and reemerging old diseases, as well as the epidemic of acquired immune deficiency syndrome (AIDS), are major public health problems that have created increased concern about infectious disease control practices, particularly in regard to blood-borne diseases such as those transmitted by the human immunodeficiency virus (HIV) and the hepatitis B virus (HBV), and diseases caused by multidrug-resistant organisms, such as *Mycobacterium tuberculosis*. However, concerns that these organisms may be highly resistant to current chemical sterilization agents and methods have largely proven to be without foundation. Several studies have demonstrated that current chemical sterilization agents and methods are effective against these microorganisms (Anderson, 1998; Rutala, Stiegel, Sarubbi, and Weber, 1997).

As will be described in this TIR, the suitability of any given liquid chemical sterilant/HLD or gaseous chemical sterilization technique for use in a particular institution depends on its compatibility with the types of items being processed; the time required for processing; and the types of toxicological, environmental, and occupational safety problems presented. These factors should be evaluated in conjunction with the documentation available in the scientific literature, the medical device manufacturer's instructions for appropriate reprocessing methods, and the labeling supplied by the liquid chemical sterilant/HLD or gaseous chemical sterilizer manufacturer.

2 Definitions and abbreviations

For the purposes of this Technical Information Report, the following definitions and abbreviations apply:

2.1 ACGIH: American Conference of Governmental Industrial Hygienists.

2.2 action level: For certain chemicals, the airborne concentration of an air contaminant, calculated as an 8-hour time-weighted average (TWA), above which particular monitoring, medical surveillance, or other stated Occupational Safety and Health Administration (OSHA) requirements apply.

2.3 bioburden: Population of viable microorganisms on a product and/or a package.

2.4 ceiling limit: According to OSHA, "the employee's exposure [to an air contaminant] which shall not be exceeded during any part of the work day. If instantaneous monitoring is not feasible, then the ceiling shall be assessed as a 15-minute time-weighted average exposure which shall not be exceeded at any time over a working day" (29 CFR 1910.1000). See also **threshold limit value**.

2.5 chemical sterilization: Process, using a chemical agent, that is designed to render a product free of viable microorganisms.

2.6 critical devices: Medical devices that are introduced into or have contact with the bloodstream or normally sterile areas of the body. Examples include, but are not limited to, implants and surgical instruments.

2.7 disinfection: Process that kills most forms of microorganisms on inanimate surfaces.

2.8 EPA: Environmental Protection Agency.

2.9 FDA: Food and Drug Administration.

2.10 General Duty Clause: Section 5(a)(1) of the Occupational Safety and Health Act of 1970. This section provides that each employer "shall furnish to each of his employees employment and a place of employment which are free from recognized hazards that are causing or are likely to cause death or serious physical harm to his employees."

2.11 high-level disinfection: Process that utilizes a sterilant for a shorter contact time than that used for sterilization and that kills all microbial organisms but not necessarily large numbers of bacterial spores.

2.12 intermediate-level disinfection: Process that utilizes an agent that kills viruses, mycobacteria, fungi, and vegetative bacteria, but not bacterial spores.

2.13 local exhaust hood: System designed to capture contaminated air and conduct it into an exhaust duct. Also termed **venting hood**.

2.14 low-level disinfection: Process that utilizes an agent that kills vegetative forms of bacteria, some fungi, and lipid viruses.

2.15 MRC: Minimum recommended concentration; minimum concentration at which the manufacturer tested the product and validated its performance.

NOTE—The term "minimum effective concentration" (MEC) is sometimes used interchangeably with "minimum recommended concentration."

2.16 MSDS: Material Safety Data Sheet.

2.17 OSHA: Occupational Safety and Health Administration.

2.18 permissible exposure limits (PELs): According to OSHA, "limits developed by OSHA to indicate the maximum airborne concentration of a contaminant to which an employee may be exposed over the duration specified by the type of PEL assigned to that contaminant" (OSHA, 1989). See also **threshold limit value**.

2.19 semicritical devices: Medical devices that contact intact mucous membranes or nonintact skin, but that do not ordinarily penetrate the blood barrier or otherwise enter normally sterile areas of the body. Examples include, but are not limited to, gastrointestinal endoscopes (transoral and transrectal) and respiratory therapy equipment.

2.20 short-term exposure limit (STEL): According to OSHA, "the employee's 15-minute time weighted average exposure which shall not be exceeded at any time during a work day unless another time period is specified [by OSHA]. If another time period is specified, the time weighted average exposure over that time period shall not be exceeded at any time during the working day" (OSHA, 1992). See also **threshold limit value**.

2.21 sterilant/sterilization agent: Physical or chemical entity, or combination of entities, that has sufficient microbicidal activity to achieve sterility under defined conditions.

2.22 sterile: Free from viable microorganisms.

NOTE—In practice, no such absolute statement regarding the absence of microorganisms can be proven.

2.23 sterility assurance level (SAL): Probability of a viable microorganism being present on a product unit after sterilization.

NOTES—

1) SAL is normally expressed as 10^{-n}.

2) A SAL of 10^{-6} means that there is less than or equal to one chance in a million that a single, viable microorganism is present on a sterilized item. 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).

2.24 sterilization: Validated process used to render a product free of all forms of viable microorganisms.

NOTE—In a sterilization process, the nature of microbiological death is described by an exponential function. Therefore, the presence of microorganisms on any individual item can be expressed in terms of probability. While this probability can be reduced to a very low number, it can never be reduced to zero.

2.25 threshold limit value (TLV®): According to ACGIH, "Threshold Limit Values (TLVs) refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse health effects" (ACGIH, 1999). Three categories of TLVs are specified by ACGIH: TLV–TWA, TLV–STEL, and TLV–ceiling (TLV–C).

> **TLV–TWA:** According to ACGIH, "the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect."
>
> **TLV–STEL:** According to ACGIH, "a 15-minute TWA exposure which should not be exceeded at any time during a workday even if the 8-hour TWA is within the TLV–TWA. Exposure above the TLV–TWA up to the STEL should not be longer than 15 minutes and should not occur more than four times per day. There should be at least 60 minutes between successive exposures in this range."
>
> **TLV–C:** According to ACGIH, "the concentration that should not be exceeded during any part of the working exposure. In conventional industrial hygiene practice if instantaneous monitoring is not feasible, then the TLV–C can be assessed by sampling over a 15-minute period except for those substances that may cause immediate irritation when exposures are short."

2.26 time-weighted average (TWA): According to OSHA, "the employee's average airborne exposure in any 8-hour work shift of a 40-hour work week which shall not be exceeded" (29 CFR 1910.1000). See also **threshold limit value**.

3 Performance and safety characteristics

3.1 General

The safety and performance characteristics of a liquid chemical sterilant/HLD or gaseous chemical sterilant can be categorized in terms of (a) its effectiveness in killing microorganisms under the prescribed conditions of use, (b) its effects on the materials and devices it is intended to sterilize or disinfect, and (c) its toxicity and potential to harm health care personnel and patients.

NOTE—The FDA clearance process for chemical sterilants addresses all of these issues (see 5).

3.2 Microbial lethality

The effectiveness of a liquid chemical sterilant/HLD or gaseous chemical sterilant is determined by its ability, under specified conditions, to kill selected microorganisms. Chemical sterilizing agents tested against bacterial spores are usually assumed to be capable of killing all forms and types of microorganisms. Chemical sterilizing agents are also tested against other microorganisms, such as mycobacteria and viruses.

"Sterilization" and "sterile" refer to absolute states. "Sterilization," for example, is often defined as a "validated process used to render a product free of all forms of viable microorganisms" (see 2.24). It is extremely difficult, however, to prove the absence of viable microorganisms. Consequently, in practice, sterility is usually described in terms of the probability of a surviving microorganism, and the nature of microbiological death in a sterilization process is described by an exponential function if the death curve exhibits log linear kinetics. While the probability of a surviving microorganism can be reduced to a very low number, it can never be reduced to zero. This probability is referred to as the sterility assurance level (SAL). It is generally accepted that a SAL of no less than 10^{-6}, which means that there is less than or equal to one chance in a million that a single, viable microorganism is present on a sterilized item, 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). Methods have been developed to determine the probability of a surviving microorganism, enabling the effectiveness of a sterilization process—its microbial lethality—to be demonstrated (see annex A).

For a manufacturer to obtain FDA clearance for the marketing of a chemical sterilant, FDA recommends that the manufacturer conduct certain tests to demonstrate that the product is effective when used as directed. Manufacturers must base their label claims and recommendations for use on the outcome of those tests (see 4.2, 4.3.1, and annex A).

3.3 Materials compatibility

Another important aspect of the safety and performance of a liquid chemical sterilant/HLD or gaseous chemical sterilant is its compatibility with materials and devices that it is intended to sterilize or disinfect. That is, the sterilant or HLD should not alter the material of a device in such a way that the device will not be safe or will not function as intended. Many materials, such as metals, alloys, and plastics and their polymers, can be adversely affected by exposure to certain chemicals and stresses. Some materials might become brittle and crack. Others, such as certain polymeric adhesives, might dissolve. Still others might swell or become distorted. Any of these effects can cause the device to malfunction or even to fail.

Medical device manufacturers should conduct tests to determine the effects of the liquid chemical sterilants/HLDs or gaseous chemical sterilants that they recommend for use on their products. The FDA recommends that manufacturers of liquid chemical sterilants/HLDs and gaseous chemical sterilization systems provide test data on materials compatibility and device functionality after repeated exposures for generic types of medical devices (see 5). Since the materials compatibility testing submitted to FDA during a 510(k) review process might not be applicable to all devices within the generic group, health care personnel should check with the reusable device manufacturer for specific information regarding the compatibility of the device with the liquid chemical sterilant/HLD or gaseous chemical sterilant. It is important that health care personnel use a liquid chemical sterilant/HLD or gaseous chemical sterilization system under the conditions and according to the instructions specified in the manufacturer's labeling, because product compatibility has been demonstrated for those conditions and cannot be ensured under other conditions.

Materials compatibility is discussed in more detail in annex B.

3.4 Toxicity

Health care personnel must be protected from hazards associated with occupational exposure to liquid chemical sterilants/HLDs and gaseous chemical sterilants. Patients must be protected from the potentially harmful effects of exposure to liquid chemical sterilant/HLD residues and gaseous chemical sterilant residues remaining on medical devices. Before clearing a liquid chemical sterilant/HLD or gaseous chemical sterilization system for marketing, FDA requires that the manufacturer provide evidence of the safety and efficacy of the product. FDA must also clear the manufacturer's labeling for the product, which includes instructions for use with adequate warnings and precautions.

Because liquid chemical sterilants/HLDs and gaseous chemical sterilants vary in their toxicity, they also vary in the potential health hazards to humans. Many liquid chemical sterilants/HLDs and gaseous chemical sterilants cause short-term health problems, such as irritation to the eyes, skin, and respiratory passages. Others—depending on exposure concentration, exposure time, or both—can pose serious long-term health hazards. The Material Safety Data Sheet (MSDS) and other relevant manufacturer or public literature on the specific product should be consulted. OSHA imposes limits on occupational exposure to various chemical sterilants/HLDs and requires manufacturers and importers to provide MSDSs with their products to inform workers of the nature of the chemical or chemical mixture and the associated risks. The MSDS must be readily accessible at all times to employees using the chemicals, and it must provide pertinent information regarding toxicity, reactivity, required protective equipment and apparel, storage, and disposal. (See 5.6 and annex E.)

4 Types of chemical sterilants and high-level disinfectants

4.1 General

This section provides general information about chemical sterilants and high-level disinfectants that are currently commercially available.[2] Sterilization/high-level disinfection processes may evolve over time, and manufacturers' label claims and instructions may change accordingly. Therefore, when considering for use or using a particular product or process, it is essential that users obtain up-to-date information and refer to the manufacturer's label directions and instructions.

4.2 Categories

Chemical sterilants and high-level disinfectants can be placed into two basic categories: (a) liquid chemical sterilants/HLDs in which the items to be sterilized or high-level disinfected are immersed manually or processed in an automated system under defined cycle conditions; and (b) gaseous chemical sterilants that are used in a sterilizer under defined cycle conditions. Whereas medical devices undergoing gaseous chemical sterilization can be packaged to maintain product sterility indefinitely, devices undergoing liquid chemical sterilization/high-level disinfection are not packaged.

All chemical sterilants/HLDs have in common the ability to kill bacterial spores. However, liquid chemical sterilization/high-level disinfection processes and gaseous chemical sterilization processes are validated by different methods. For most liquid chemical sterilants/HLDs, the sterilization claim on the label represents the contact conditions necessary for the liquid sterilant to pass the Association of Official Analytical Chemists (AOAC) Sporicidal Test (AOAC, 1995) as a sterilant, not necessarily the contact conditions needed to sterilize a reusable critical medical device (see annex A). Most, but not all, liquid chemical sterilants are principally used as high-level disinfectants or to sterilize reusable medical devices that are not amenable to physical sterilization processes (e.g., steam) or gaseous chemical sterilization processes (e.g., ethylene oxide and other chemical vapors).

4.3 Liquid chemical sterilants/high-level disinfectants

4.3.1 General characteristics

Some liquid chemical sterilants are labeled for use as both sterilants and high-level disinfectants, with sterilization requiring a longer contact time. Although most liquid chemical sterilants/HLDs cleared by FDA are labeled for use as both sterilants and high-level disinfectants, these products are most often used as high-level disinfectants. For each product, the appropriate conditions for use are given on its label. The conditions given on the product label for high-level disinfection or sterilization are determined by the manufacturer, using FDA-recommended testing protocols (FDA, 2000). The labeled conditions for high-level disinfection are the time and temperature required to achieve a

[2] This section covers those chemical sterilants known to be commercially available at the time of this writing. For up-to-date information on sterilants and high-level disinfectants cleared by FDA, contact either the Chief, Infection Control Devices Branch (HFZ-480), Center for Devices and Radiological Health, FDA, 9200 Corporate Blvd., Rockville, MD 20850 (301/443-8913); or FDA's Web site at http://www.fda.gov/cdrh/ode/germlab.html. The list provided at FDA's Web site identifies the liquid chemical sterilants and high-level disinfectants cleared by FDA in a 510(k) with general claims for processing reusable medical and dental devices. It does not include preamendment products, FDA-cleared germicides dedicated to specific devices such as hemodialyzers or hemodialyzer machines, or gaseous chemical sterilization systems.

six-log reduction of an appropriate mycobacterium species, such as *M. bovis BCG* or *M. terrae*, that has resistance characteristics similar to those of the human strain of *M. tuberculosis,* under the conditions specified in the recommended test protocol. For most FDA-cleared liquid chemical sterilants/HLDs, the labeled contact conditions for sterilization are the contact conditions required to pass the AOAC Sporicidal Test as a sterilant.

Some liquid chemical sterilant/HLD products are designed for single use; others, for reuse. The user should read the labeling to determine how to use the product correctly.

Liquid chemical sterilants/HLDs are commonly provided as formulations containing one or more sporicidal agents designated as "active" ingredients and one or more other ingredients designated as "inert." Although "inert" is the commonly used term, it is something of a misnomer because these ingredients can be important to the sterilizing process and can include anticorrosive agents to improve the materials compatibility of the sterilant, detergents to increase wettability and soil removal, and buffers or activating agents to adjust the pH of the solution and ensure the potency of the active agent. Frequently, the inert ingredients are added at the time of use, and it is necessary for the user to ensure that the inert and active ingredients are thoroughly mixed. Some products are available as "ready-to-use" solutions; others are available as concentrates that must be further diluted with water to achieve the proper "use dilution."

Typically, an item is immersed in the liquid sterilant/HLD for a defined period of time at a set temperature; these parameters are determined by the manufacturer and indicated in the product labeling. ("Labeling," as the term is used here and in its regulatory sense, includes not only information printed on, or affixed to, the product container, but also any accompanying instructions for use and any documentation, such as advertising, in which claims are made for the product.) Some products are intended for manual use in trays or other containers; it is necessary for the user to ensure that the sterilant concentration, exposure time, and exposure temperature are correct and to manually rinse the sterilized or high-level disinfected items using aseptic technique. Other products are provided for use in automated systems that circulate the sterilant around and through the items to be processed. These systems control the exposure conditions; some also provide rinsing with filtered water. Whether the sterilization/high-level disinfection process is manual or automated, items to be sterilized/high-level disinfected in these systems are not packaged. Therefore, sterilized/high-level disinfected items must be handled with special care to avoid contamination before patient use.

All items processed with liquid chemical sterilants/HLDs should be rinsed to reduce chemical residues to safe levels. The microbial quality of the solution used to rinse items processed by liquid chemical sterilants/HLDs is an important aspect of the sterilization/high-level disinfection process. Users should follow the recommendations of the device manufacturer and the sterilant manufacturer for the microbial quality of the solution to be used for rinsing. Unless the device is rinsed with a sterile solution, the sterility of the device will be compromised. For further information pertaining to the microbial quality of rinse water and water filtration, see ASTM (1990), Block and Schwartzbrod (1989), Blosse, Boulter, and Sundaram (1998), EPA (1996), Floyd and Sharp (1977), Franson (1992), HIMA (1982), Howard and Duberstein (1980), Hurst (1991), ISO (1998), Levy and Leahy (1991), PDA (1997), and USP (1995).

To obtain FDA clearance, manufacturers of liquid chemical sterilants/HLDs must provide chemical indicators for use in monitoring their products. Biological indicators intended for use with liquid chemical sterilants/HLDs have characteristics that differ from those of biological indicators intended for use with other sterilization systems such as steam and EO. It may be necessary to use these biological indicators, when provided, in conjunction with chemical indicators. Users should follow the manufacturer's labeled recommendations for use of the chemical indicator and, if applicable, the biological indicator provided for use with the liquid chemical sterilant/HLD.

Many liquid chemical sterilant/HLD formulations are now available commercially. Products containing the following active ingredients are marketed under various brand names and in various concentrations: glutaraldehyde, hydrogen peroxide, and combinations of peracetic acid and hydrogen peroxide. A list of liquid chemical sterilant/HLD products that have been cleared for marketing by FDA and are available commercially can be found on the FDA/Center for Devices and Radiological Health (CDRH) Internet Home Page at http://www.fda.gov/cdrh/ode/germlab.html. This list is updated as new products are cleared and includes the concentration of active ingredient(s), the sterilization and high-level disinfection contact times and temperatures, and the maximum reuse time period for each product. The list provided at FDA's Web site identifies the liquid chemical sterilants/HLDs cleared by FDA in a 510(k) with general claims for processing reusable medical and dental devices. It does not include preamendment products, FDA-cleared sterilants/HLDs dedicated to specific devices such as hemodialyzers or hemodialyzer machines, or gaseous chemical sterilization systems.

4.3.2 Glutaraldehyde

The biocidal properties of 2% glutaraldehyde in alkaline aqueous solution were discovered in the early 1960s (Borick, Dondershine, and Chandler, 1964). This basic formulation was later refined to include, when appropriate, corrosion inhibitors, wetting agents, and buffers to control the pH of the solution. Other formulations with increased sterilant concentrations (e.g., 3.4%) also have been developed.

Several companies now produce glutaraldehyde-based liquid sterilants and disinfectants. These products are sometimes referred to as either “acid glutaraldehyde” or “alkaline glutaraldehyde.” Products designated as “alkaline” are usually supplied in two parts (active glutaraldehyde solution and activator buffer), which require mixing before use to impart an alkaline pH to the solution (a pH of approximately 8). Those designated as “acid” usually do not require an activator.

Glutaraldehyde-based sterilants usually are used as high-level disinfectants for semicritical devices. Conditions for high-level disinfection generally range from 20 minutes (min) to 90 min at 20° C to 25° C (68° F to 77° F), depending on the product formulation and glutaraldehyde concentration (see table 1). For currently available products, the contact time for sterilization is 10 hours at temperatures ranging from 20° C to 25° C (68° F to 77° F), depending on the product formulation and glutaraldehyde concentration.

Table 1—Labeled contact conditions for high-level disinfection for FDA-cleared glutaraldehyde products

Glutaraldehyde Solution	Contact Conditions
2.4%–2.6% glutaraldehyde solutions without surfactants	20° C–25° C (68° F–77° F) 45 min
2.4%–2.5% glutaraldehyde solutions with surfactants	20° C–25° C (68° F–77° F) 45–90 min
3.0%–3.4% glutaraldehyde solutions with surfactants	20° C–25° C (68° F–77° F) 20–90 min

Several professional organizations recommend minimum contact times for high-level disinfection using 2% glutaraldehyde that differ from those resulting from FDA’s product clearance process (table 1) (see annex C). Facilities using contact times and/or conditions other than those specified on the product label should document their review and acceptance of the scientific justification for the different contact time/conditions. The infection control director and the risk management director of the facility should be among those involved in the review and acceptance.

Because the health care industry has used glutaraldehyde for more than 30 years to disinfect and sterilize medical devices, there is a large amount of information in the literature regarding its mechanism of action, the role of pH control, its compatibility with the various materials used to manufacture medical devices, the effect of temperature on the rate of microbial kill, and the procedures that should be used for the safe handling of glutaraldehyde solutions (AAMI, 1996a; Jordan, 1995; Martin and Reuchelderfer, 1994; Rubbo, Gardner, and Webb, 1967; Russell, 1994; Stonehill, Krop, and Borick, 1963). To ensure the safe and effective use of a particular product, however, it is most important that users consult the labeling because the directions vary according to the manufacturer’s formulation.

Glutaraldehyde-based products can be used in automated or manual high-level disinfection processes. Many automated reprocessors are equipped with temperature-control devices, computerized reprocessing cycles, and bacteria-retentive filters for rinse water, as well as filters for removing suspended materials from the reused disinfectant solution. It should be noted that formulations containing surfactants might not be suitable for automated systems because of the potential for foaming.

Glutaraldehyde is compatible with most device materials used today and can be used to process medical devices containing heat-sensitive materials. Most glutaraldehyde-based instrument sterilants are labeled for reuse for 14 to 28 days. During the recommended reuse period, the concentration of the glutaraldehyde in the solution should be tested with the test strips recommended by the manufacturer at least once each day that the solution is used. If the solution falls below its minimum recommended concentration, it should be discarded regardless of how many days the solution has been in use.

Vapor generated from glutaraldehyde can be irritating to the respiratory tract, and current information suggests that it may aggravate preexisting respiratory conditions such as asthma. For that reason, all glutaraldehyde solutions should be used in well-ventilated areas or in freestanding or vented chemical fume hoods. The American Conference of Governmental Industrial Hygienists (ACGIH) recommends a ceiling limit of 0.05 parts per million (ppm) for occupational exposure to glutaraldehyde vapors. Even in low concentrations, there is a potential for liquid glutaraldehyde to be a contact sensitizer through the dermal route of exposure. Ocular contact with aqueous solutions containing 2% or higher concentrations of glutaraldehyde can cause severe eye irritation and damage. (See also AAMI, 1996a.)

4.3.3 Peracetic acid/hydrogen peroxide solutions

Peracetic acid solutions are stabilized solutions of hydrogen peroxide, acetic acid, and peracetic acid and have a strong, vinegar-like odor.

The strong microbicidal effects and broad-spectrum activity of peracetic acid (also referred to as peroxyacetic acid) have been known since the early 1900s (Freer and Novy, 1902; Block, 1991). Aqueous solutions of peracetic acid contain hydrogen peroxide in concentrations that are related to the concentration of peracetic acid. Peracetic acid/hydrogen peroxide solutions can be formulated to include buffers, surfactants, and metal anticorrosives for their specific applications. To ensure compatibility, users are advised to consult with the device (instrument) manufacturer before using the product.

The ACGIH-recommended threshold limit value (TLV) for hydrogen peroxide is 1 ppm as an 8-hour time-weighted average (TWA). No limits have been established for peracetic acid; for acetic acid, however, ACGIH recommends a 10-ppm TWA and a 15-ppm STEL. (There is no known way to measure peracetic acid vapor levels because it decomposes into hydrogen peroxide and acetic acid.) Vapors from peracetic acid/hydrogen peroxide solutions can be irritating to the nose, throat, and lungs. Contact with the liquid can cause skin burns and eye damage. Hydrogen peroxide is listed as a Group 3 carcinogen ("unclassifiable as to carcinogenicity to humans") by the International Agency for Research on Cancer (IARC) and as an animal carcinogen by ACGIH.

NOTE—IARC and ACGIH carcinogen classifications have specific meanings and are based on specific types of evidence. For an explanation of the IARC carcinogen classifications, see IARC (1999) and/or the IARC Web site at http://www.iarc.fr. For an explanation of ACGIH carcinogen classifications, see ACGIH (1999).

One peracetic acid formulation, which has been available since 1988, is designed for single use in an automated system. This formulation is FDA-cleared for the sterilization of cleaned, reusable medical devices. In this system, concentrated (35%) liquid peracetic acid is diluted with a buffer, surfactant, and anticorrosive dry powder to its 0.2% (2000 ppm) use dilution (Malchesky, 1993). The labeled contact conditions for sterilization are 12 min at 50° C to 56° C (122° F to 133° F). During the sterilization cycle, time and temperature are automatically controlled and monitored. The cycle includes rinsing with sterile water produced by passing tap water through a 0.2-micron filtration membrane. The efficacy of this filtration process depends on the quality of the incoming tap water (EPA, 1996). The purpose of rinsing is to remove sterilant residues. Although the actual cycle time depends on inlet water temperature and pressure, the nominal total cycle time is about 30 min. Biological and chemical indicators designed for this system are available from the manufacturer. Department of Transportation (DOT) shipping restrictions apply to concentrated solutions of peracetic acid (including 35% to 43% solutions). DOT categorizes these solutions as organic peroxides and corrosive. Special handling procedures are required (see the MSDS).

Another available formulation is provided prediluted and ready to use. This formulation is used to sterilize or high-level disinfect cleaned medical devices. The formulation contains approximately 1% hydrogen peroxide and 0.08% peracetic acid. At 20° C (68° F), sterilization time is 8 hours, and high-level disinfection time is 25 min. The formulation is reusable up to 14 days. During the recommended reuse period, the concentration of the hydrogen peroxide and peracetic acid in the solution should be checked with the test strips recommended by the manufacturer at least once each day that the solution is used. Chemical test strips are available to measure the chemical concentrations of the active ingredients.

Unlike the more concentrated solutions, the ready-to-use solution is not a skin irritant and does not cause dermal sensitization. Toxic inhalation effects have not been shown in testing. However, the formulation is corrosive to ocular tissue.

4.3.4 Hydrogen peroxide solutions

A hydrogen peroxide product has been recently cleared by FDA for use as a liquid chemical sterilant and high-level disinfectant on heat-sensitive medical devices (e.g., flexible endoscopes). The product is used as a high-level disinfectant at contact conditions of 30 min at 20° C (68° F); for sterilization, the labeled contact conditions are 6 hours at 20° C (68° F). The solution contains 7.5% hydrogen peroxide, 0.85% phosphoric acid, and 91.65% inert ingredients. (The grade and concentration of this product differ from the grade and concentration of the product used in the household setting.)

The product has a reuse life of up to 21 days. During the recommended reuse period, the concentration of the hydrogen peroxide in the solution should be checked with the test strips recommended by the manufacturer before each reprocessing cycle. A chemical indicator (test strip) is available to determine whether the concentration of the active ingredient (hydrogen peroxide) is at or above the minimum recommended concentration of 6.0%.

The currently available hydrogen peroxide product can be used in automated or manual high-level disinfection processes. To ensure that their particular model is fully compatible with the solution, users are advised to consult the reprocessor manufacturer before using the product.

This hydrogen peroxide product may cause cosmetic damage (e.g., discoloration) to devices, but it is not known to cause functional damage. However, it is recommended that before using the solution, users should consult with instrument manufacturers to ensure device compatibility.

The ACGIH-recommended TLV for hydrogen peroxide is 1 ppm as an 8-hour TWA. Hydrogen peroxide is listed as a Group 3 carcinogen ("unclassifiable as to carcinogenicity to humans") by the IARC and as an animal carcinogen by ACGIH.

NOTE—IARC and ACGIH carcinogen classifications have specific meanings and are based on specific types of evidence. For an explanation of the IARC carcinogen classifications, see IARC (1999) and/or the IARC Web site at http://www.iarc.fr. For an explanation of ACGIH carcinogen classifications, see ACGIH (1999).

4.4 Chemical sterilant gases

4.4.1 General characteristics

The most widely used chemical sterilant gas is EO. Ethylene oxide gas is an effective sterilant, but toxicity concerns and regulatory constraints have spurred interest in alternative sterilant gases. (See AAMI [1999b] for additional information on EO sterilization.) Formaldehyde/alcohol combinations have been in use for some time. Also, new gaseous sterilization systems, such as those using gas plasma with hydrogen peroxide, have been developed and introduced for industrial and/or hospital applications. All chemical sterilant gases are intended to be used in enclosed sterilization chambers under cycle conditions designed and specified by the manufacturer.

4.4.2 Formaldehyde/alcohol

Small "table-top" sterilizers employing a sterilant mixture of alcohol and formaldehyde have been used in dentistry and other health care applications for sterilizing dental instruments and related devices. In this method, known as the unsaturated chemical vapor sterilization process, a sterilizing solution composed of various alcohols, water, and a small percentage of formaldehyde is introduced into a heated chamber, where it is vaporized. The vapors initially condense as the items reach processing temperature (vaporization phase). Nominal cycle parameters are 20 min exposure at a temperature of 132° C (270° F) and a pressure of 20 pounds per square inch gauge (psig). A shorter flash cycle is available on some units for a single, non-lumened device. The user should follow the recommendations provided by the manufacturer in the labeling. Incorporation of a post-process purge (of approximately 7 min) and an emission filter, which is available on newer models, is recommended to reduce residual vapors within the chamber and limit environmental exposure.

This process will not corrode metal instruments or dull cutting edges, and no drying phase is necessary. The process is not recommended for liquids or agars, linens or textiles, items contained in dense packs, nylon tubing or sealed containers, or items that cannot withstand elevated temperatures. Both biological and chemical indicators are available for monitoring the process.

The current OSHA occupational exposure limit for formaldehyde is 0.75 ppm as an 8-hour TWA and 2.0 ppm as a 15-min STEL, with an action level of 0.5 ppm as an 8-hour TWA (29 CFR 1910.1048). ACGIH recommends a ceiling limit of 0.3 ppm for formaldehyde. Formaldehyde is listed as a Group 2A carcinogen ("probably carcinogenic to humans") by the IARC and as a suspected human carcinogen by ACGIH. The exposure limit for alcohol varies with the particular type of alcohol. The user should consult the label to identify the constituent alcohols and should refer to OSHA for the applicable occupational exposure limits. The spent sterilant solution (condensate) should be disposed of in accordance with state and local regulations.

NOTE—IARC and ACGIH carcinogen classifications have specific meanings and are based on specific types of evidence. For an explanation of the IARC carcinogen classifications, see IARC (1999) and/or the IARC Web site at http://www.iarc.fr. For an explanation of ACGIH carcinogen classifications, see ACGIH (1999).

For further information about formaldehyde/alcohol sterilization, see Guggenheim (1995), Lyon and Devine (1974), and Miller and Sheldrake (1991).

4.4.3 Gas plasma sterilization

The newly developed gas plasma sterilization processes are particularly suited for sterilizing heat- and moisture-sensitive materials because temperatures within the load currently do not exceed 50° C (122° F) and sterilization occurs in a low-moisture environment. One FDA-cleared gas plasma sterilizer is currently marketed in the United States.

This system uses a pretreatment chemical exposure followed by generation of a low-temperature plasma. It involves the following sequential steps: Articles to be sterilized are placed into the sterilization chamber, the chamber is closed, and a vacuum is drawn. An aqueous solution of hydrogen peroxide is then injected into the chamber, where it vaporizes and surrounds the items to be sterilized. After a period of hydrogen peroxide diffusion, the pressure is reduced in the chamber, and the formation of a low-temperature gas plasma is initiated by applying radiofrequency

(RF) energy to create an electric field. In the plasma state, the hydrogen peroxide vapor breaks apart into reactive species that include free radicals. The combined use of hydrogen peroxide vapor and plasma sterilizes items in the chamber in approximately 75 min; no toxic residues are left. Following the reaction, the activated components lose their high energy and recombine to form primarily oxygen and water vapor as byproducts. When the process is complete, the RF energy is turned off, the vacuum is released, and the chamber is returned to atmospheric pressure by venting through a HEPA filter. Items inside the chamber are now ready for immediate use. This system has been cleared by FDA for use in sterilizing metal and plastic instruments, including lumened devices having a specified minimum inside diameter and a specified maximum length.

The items to be sterilized in this system should be thoroughly cleaned and dried before sterilization. Items should be wrapped in nonwoven polypropylene wraps or Tyvek®/Mylar® packaging. Liquids and cellulosics cannot be processed in this system. Chemical and biological indicators are available from the sterilizer manufacturer for monitoring the sterilization process.

The ACGIH-recommended TLV for hydrogen peroxide is 1 ppm as an 8-hour TWA. Hydrogen peroxide is listed as a Group 3 carcinogen ("unclassifiable as to carcinogenicity to humans") by the IARC and as an animal carcinogen by ACGIH.

NOTE—IARC and ACGIH carcinogen classifications have specific meanings and are based on specific types of evidence. For an explanation of the IARC carcinogen classifications, see IARC (1999) and/or the IARC Web site at http://www.iarc.fr. For an explanation of ACGIH carcinogen classifications, see ACGIH (1999).

5 Government regulation

5.1 General

Chemical sterilants are regulated by the Environmental Protection Agency (EPA), the Food and Drug Administration (FDA), the Occupational Safety and Health Administration (OSHA), and state and local governments. The extent of regulation by each agency depends on the type and intended use of the chemical sterilant.

Before passage of the Food Quality Protection Act of 1996 (FQPA), both EPA and FDA regulated liquid chemical sterilants/HLDs used on medical devices. Under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), EPA is responsible for registering pesticides before they are sold and for ensuring that, when used according to label directions, they are effective and do not present unreasonable risks to human health or the environment. The FQPA excluded liquid chemical sterilants/HLDs used to reprocess critical and semicritical medical devices from the FIFRA definition of pesticide. Consequently, FDA now has *sole* regulatory jurisdiction over these liquid chemical sterilants/HLDs. The FQPA did not affect the regulation of general-purpose disinfectants.

Before a liquid chemical sterilant/HLD product can be introduced into interstate commerce, the manufacturer must submit a premarket notification to FDA in accordance with section 510(k) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), and receive premarket clearance for the product. Although FDA clears new products for marketing, it does not endorse any product or conduct independent testing of a product's safety and performance characteristics. The agency relies exclusively on the manufacturer's safety and efficacy data during product evaluation.

FDA also regulates sterilization systems sold to health care facilities that use gaseous chemical sterilants, including EO, formaldehyde/alcohol, hydrogen peroxide, and gas plasma. The manufacturer of a gaseous chemical sterilizer intended for use by health care facilities must submit a premarket notification [510(k)] to FDA and must receive market clearance before the sterilizer can be introduced into interstate commerce. The EPA regulates EO gas, but not the other gaseous agents used in sterilizers. More information on FDA's premarket notification requirements for sterilizers can be found in FDA (1993).

OSHA regulates occupational exposure to toxic chemicals that might be present or used in the workplace. Consequently, this agency is empowered to establish limits on occupational exposure to chemical sterilants/HLDs and to impose labeling requirements on manufacturers.

State and local health agencies also regulate certain aspects of the use and disposal of chemical sterilants/HLDs. Such regulations must be at least as stringent as federal requirements; in some cases, state and local requirements are *more* stringent than federal requirements.

5.2 FDA regulation of medical devices

5.2.1 Statutory authority

FDA regulates medical devices under the authority of the FD&C Act. Under the Medical Device Amendments of 1976, as amended by the Safe Medical Devices Act of 1990 and the Food and Drug Administration Modernization Act of 1997 (FDAMA), devices are to be classified into one of three regulatory classes, according to the amount of

regulation necessary to provide a reasonable assurance of safety and effectiveness: Class I (general controls), Class II (special controls), or Class III (premarket approval [PMA]).

5.2.2 FDA regulatory classification of medical devices

5.2.2.1 Classification process

Most generic types of medical devices that were on the market before 28 May 1976 (the date of passage of the Medical Device Amendments of 1976) have been classified by FDA into one of the three regulatory classes through issuance of classification regulations. (Such devices are referred to as "preamendment" devices.) Devices introduced into interstate commerce for the first time on or after 28 May 1976 are classified through the premarket notification [510(k)] process. Manufacturers who intend to market a new or significantly modified device must submit a premarket notification application containing information and proposed labeling that allows FDA to determine whether the new device is "substantially equivalent" (as defined in the FD&C Act) to a legally marketed device (i.e., a preamendment device or a device previously determined to be substantially equivalent to a legally marketed device). If FDA determines that a new or modified device is "substantially equivalent," the new device will be regulated in the same manner as the device to which it was found to be substantially equivalent.

5.2.2.2 Class I devices

Class I devices are judged by FDA to present relatively low risk to patients. The "general controls" provisions of the FD&C Act are considered sufficient to ensure the safety and effectiveness of these devices. Under general controls, manufacturers are required, among other things, to register their establishments and list their products with FDA and to comply with the good manufacturing practice (GMP) requirements set forth in the Quality System regulation (21 CFR 820). These requirements represent the least stringent level of regulation. Ultrasonic cleaners and most hand-held surgical instruments are examples of Class I devices.

Some Class I devices were specifically exempted, by regulation, from 510(k) requirements. However, under the FDAMA, all Class I devices are exempt from premarket notification requirements unless the device is intended for a use of substantial importance in preventing impairment of human health or unless it presents a potential unreasonable risk of illness or injury. Class I devices that are not exempt have been specifically identified as "Reserved" Class I devices (FDA 1998a).

5.2.2.3 Class II devices

Class II devices present relatively greater risk to patients, and general controls alone are considered insufficient to provide reasonable assurance of their safety and effectiveness. However, sufficient information exists to establish special controls to provide such assurance. Special controls could include performance standards, postmarket surveillance, development and dissemination of guidelines, and FDA guidances for 510(k) submissions. Class II devices include EO sterilizers, EO aerators, steam sterilizers, biological indicators, chemical indicators, and sterilization wraps. (Sterilizers, biological and chemical indicators, and sterilization wraps are considered medical devices when intended for use in a health care facility or by a health care provider.)

Before the FDAMA, a Class II device had to be reclassified to Class I in order for it to be exempted from 510(k) requirements. Under the provisions of the FDAMA, however, FDA has determined that certain Class II devices can be exempted from 510(k) requirements and has published a list of Class II devices that are now exempt from premarket notification (FDA 1998b). Additional Class II devices might be exempted by FDA in the future, based on its own initiative or in response to a petition from an interested party.

It should be noted that standards published by such organizations as the American National Standards Institute, the American Society for Testing and Materials, and AAMI are *voluntary* standards. Manufacturers are not legally obligated to comply with such voluntary standards unless they claim to do so. However, as directed by the FDAMA, the FDA has published lists of national and international voluntary standards that the agency will recognize in the review of premarket notification submissions and applications for premarket approval (FDA 1998c, FDA 1998d). Manufacturers may submit a "Declaration of Conformity" to one or more of these recognized standards, as appropriate, in lieu of data in a 510(k) submission.

5.2.2.4 Class III devices

Class III devices are life-sustaining or life-supporting devices, devices that have uses of substantial importance in preventing impairment of human health, or devices that present potential unreasonable risks of illness or injury, and for which there is insufficient information to support classifying them into Class I or Class II. Class III devices are subject to premarket approval, the most stringent level of regulation. Manufacturers of Class III devices are required to submit PMA applications to FDA before they can market such devices. Examples of Class III devices are heart valves and pacemakers.

5.3 History of FDA regulation of liquid chemical sterilants/high-level disinfectants

In 1980, when other general hospital and personal-use devices were classified (FDA 1980), liquid chemical germicides were not included. In subsequent years, FDA actively regulated only those liquid chemical germicides (sterilants and disinfectants) that were used as accessories to specific Class II devices, such as hemodialyzers. The FDA began actively regulating all liquid chemical germicides in the early 1990s, following publication in 1992 of an FDA guidance document for liquid chemical germicides.

If liquid chemical germicides were considered as accessories to other medical devices, then they would be in the same regulatory class as the primary medical device. Thus, the same liquid chemical germicide product could be regulated as a Class I, Class II, or 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. The FDA also determined that two categories of liquid chemical germicides existed:

a) *liquid chemical sterilants/HLDs*, which are intended for use as the terminal step in processing critical and semicritical medical devices before patient use;

b) *general-purpose disinfectants*, which are intended to process noncritical medical devices and medical equipment surfaces and which can be used to preclean or decontaminate critical or semicritical devices before terminal sterilization or high-level disinfection.

FDA uses the Spaulding classification to determine whether a medical device is a critical, semicritical, or noncritical device. Spaulding divided medical instruments and equipment into three categories based on the risk of infection from contamination on the device (Spaulding, 1972). *Critical devices* are those that are introduced directly into the human body, either into or in contact with the bloodstream or other normally sterile areas of the body. Critical devices present a high degree of risk of transmission of infection if contaminated and, therefore, must be sterile. *Semicritical devices* are those that contact intact mucous membranes or nonintact skin during use but do not usually penetrate the blood barrier or other normally sterile areas. If a semicritical device cannot be sterilized, it must be subjected to a high-level disinfection process in which a sterilant is used but for a shorter exposure time than required to achieve sterilization. *Noncritical devices or instruments*, which pose the lowest risk of transmission of infection, are those that usually contact only intact skin; these devices must be thoroughly cleaned and might require intermediate or low-level disinfection.

In July 1995, FDA's General Hospital and Personal Use Devices Advisory Panel recommended that liquid chemical sterilants/HLDs 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 requirements, but not from GMP requirements. Proposed rules classifying the liquid chemical germicides were published in the *Federal Register* in November 1998 (FDA 1998e). The final rule classifying these products was published on 8 June 2000 (FDA 2000).

5.4 Current FDA regulation of liquid chemical sterilants/high-level disinfectants

5.4.1 Premarket notification submissions

Certain administrative-type information is required to be included in all premarket notification submissions. For liquid chemical sterilants/HLDs, manufacturers are also requested to provide information describing (a) the chemical and physical properties of the sterilant product and its active and inert ingredients, (b) the product container(s) and the compatibility of the sterilant and container material(s), (c) any accessories or containers specified for use with the sterilant, (d) product stability, (e) microbicidal efficacy, (f) biocompatibility (residues and toxicity), (g) compatibility with materials and devices with which the product is to be used, and (h) the chemical indicator systems to be used to monitor the concentration of the active ingredients of germicide products with reuse claims.

Health care personnel or manufacturers seeking additional information on premarket notification submissions for liquid chemical sterilants/HLDs should consult FDA's guidance document on liquid chemical sterilants/HLDs. A revised draft document was published for public comment on 18 December 1997. The final version of the guidance document (FDA 2000), which reflects implementation of the Food Quality Protection Act (FQPA) and FDA's consideration of public comments, was published on 3 January 2000 and is available on the CDRH Internet Home Page at http://www.fda.gov/cdrh/ode/lcgguide.html.

5.4.2 Labeling

As a result of enactment of the FQPA, EPA claims will no longer be allowed on liquid chemical sterilant/HLD products regulated only by FDA. As described in EPA PR Notice 98-2 (EPA 1998), manufacturers of products with claims regulated only by FDA (i.e., liquid chemical sterilants/HLDs labeled for use on critical and semicritical medical devices) are required to remove all EPA references from the labeling, including the EPA registration number and the EPA establishment number. Manufacturers are also required to remove all FDA references from the labeling of products regulated only by EPA.

All FDA-regulated products, including liquid chemical sterilants/HLDs, must be properly labeled in accordance with FDA's general labeling regulation (21 CFR 801), including the specific requirements for adequate directions for use (21 CFR 801.5). Terms such as "sporicidal," "tuberculocidal," "fungicidal," "bactericidal," and "virucidal," which are EPA-permitted claims, should not appear in the labeling for liquid chemical sterilant products. It has long been an FDA policy that, unless proven by clinical trials, labeling should not contain references to specific diseases or specific microorganisms. The user should be able to infer the microbicidal efficacy of a sterilant product by examining the FDA-cleared claims for the product, such as sterilization or high-level disinfection.

Users can obtain information about labeling requirements, as well as information about premarket notification submissions for cleared chemical sterilant products or sterilizing systems, from the CDRH Internet Home Page at http://www.fda.gov/cdrh; the CDRH Division of Small Manufacturers Assistance (DSMA) Home Page at http://www.fda.gov/cdrh/dsma/dsmamain.html#contents; DSMA's Facts-On-Demand (800/899-0381); or the Chief of the Infection Control Devices Branch (HFZ-480), Office of Device Evaluation, Center for Devices and Radiological Health, Food and Drug Administration, 9200 Corporate Blvd., Rockville, MD 20850 (301/443-8913).

5.5 FDA medical device reporting (MDR) regulation

The medical device reporting (MDR) regulation (21 CFR 803) requires medical device manufacturers and distributors to report to FDA any deaths, serious injuries, and device malfunctions that could result in patient injury or death. The regulation also requires device user facilities (i.e., hospitals, nursing homes, ambulatory care facilities, and outpatient treatment and diagnostic facilities) to report deaths to both FDA and the device manufacturer and to report serious injuries to the manufacturer. The MDR requirements are summarized in table 2.

Table 2—Summary of MDR requirements*

Reporter	Report What?	To Whom?	When?
User facility	Deaths	FDA and manufacturer	Within 10 work days
	Serious injuries	Manufacturer; FDA only if manufacturer unknown	Within 10 work days
	Semiannual reports of deaths and serious injuries	FDA	1 January and 1 July
Manufacturer	30-day reports of deaths, serious injuries, and malfunctions	FDA	30 days from becoming aware
	Baseline report to identify and provide basic data on each device that is subject of a report	FDA	With 30-day report when device is reported for first time
	5-day report on events that require immediate remedial action and on other types of events designated by FDA	FDA	Within 5 work days
	Annual certification of compliance with regulation	FDA	When firm submits annual registration

*From: FDA. *Medical device reporting: An overview*. April 1996.

If an event reportable under the MDR regulation should occur in connection with a liquid chemical sterilant/HLD or a gaseous chemical sterilization system, the user should report the event to the sterilant or sterilizer manufacturer as well as to the reusable device manufacturer. If the event does not qualify for reporting under the MDR regulation, it should be reported through FDA's voluntary MedWatch Reporting Program. Annex D provides samples of MDR mandatory report forms and MedWatch voluntary report forms. Additional information on MDR and MedWatch reporting can be found on the FDA Internet Home Page at http://www.fda.gov/cdrh/mdr.html and http://www.fda.gov/medwatch, respectively.

5.6 OSHA regulation of chemical sterilants

5.6.1 General

Under the Occupational Safety and Health Act, OSHA regulates occupational exposure to chemicals that are present or used in the workplace. Under its Hazard Communication Standard, OSHA also requires manufacturers of chemicals to provide users with Material Safety Data Sheets (MSDSs). These regulations are applicable to chemical sterilants.

5.6.2 Occupational exposure limits

OSHA has established occupational exposure limits for several agents used in liquid chemical sterilant/HLD formulations and gaseous chemical sterilization systems. Employers are required by law to ensure compliance with these limits by implementing engineering controls, defining procedures for safe employee work practices, establishing medical surveillance programs, providing respiratory protection, and taking other measures to the extent specified by OSHA. In addition, product manufacturers may be subject to certain labeling requirements.

Limits established by OSHA for airborne contaminants, including some liquid chemical sterilant/HLD and gaseous sterilant chemicals, are set forth in 29 CFR 1910.1000. Separate standards limiting occupational exposure to EO and formaldehyde are set forth in 29 CFR 1910.1047 and 29 CFR 1910.1048, respectively. In 1989, OSHA adopted a final rule for air contaminants in which permissible exposure limits (PELs) for hundreds of chemicals were revised or added to the Air Contaminants Standard in 29 CFR 1910.1000 (OSHA, 1989). In 1992, the 11th Circuit Court of Appeals ruled that OSHA did not sufficiently demonstrate that the new PELs were necessary or feasible. As a result of the Court's decision to vacate the new limits, OSHA was forced to return to the original limits published in 1971. However, OSHA can invoke the General Duty Clause of the Occupational Safety and Health Act of 1970 to regulate employee exposure to hazardous chemicals for which OSHA-established limits do not exist. For example, before 1989, the Air Contaminants Standard did not include exposure levels for glutaraldehyde, and there are no current OSHA-established exposure limits for glutaraldehyde. However, OSHA has invoked the General Duty Clause to regulate employee exposure and has recommended that exposures be controlled to the ACGIH-recommended TLVs for glutaraldehyde (table 3). Additionally, states with federally approved state OSHA programs may independently decide to enforce the PELs originally promulgated in the 1989 rule for air contaminants.

Table 3—Occupational exposure limits for some chemical sterilants

Chemical Agent	OSHA PEL	ACGIH TLV
Alcohols	Various*	Various*
Formaldehyde	0.75 ppm TWA 2 ppm STEL 0.5 ppm AL	0.3 ppm ceiling
Glutaraldehyde	None**	0.05 ppm ceiling
Hydrogen peroxide	1 ppm TWA 1.4 mg/m^3 TWA	1 ppm TWA
Peracetic acid	None***	None****

* Various types of alcohol are used in sterilant formulations, and the occupational exposure limits vary. Refer to the product label for the active ingredients and consult the latest ACGIH recommendations and OSHA regulations.

** No exposure limits have been established by OSHA. However, OSHA can invoke the General Duty Clause of the Occupational Safety and Health Act of 1970 to regulate exposure to glutaraldehyde and has recommended that the ACGIH TLVs be followed.

*** However, there is an OSHA PEL for acetic acid (a byproduct of peracetic acid): 10 ppm TWA (25 mg/m^3 TWA).

**** However, there are ACGIH TLVs for acetic acid (a byproduct of peracetic acid): 10 ppm TWA; 15 ppm STEL.

Limits on occupational exposure to chemical agents are commonly defined in terms of the maximum amount of chemical to which an employee can be exposed over a specified period of time. For example, OSHA mandates PELs calculated as an 8-hour time-weighted average (TWA) exposure. For some chemicals, a "short-term exposure limit" (STEL), which is based on a 15-minute exposure, has been established. For certain chemicals, including EO and formaldehyde, OSHA has established an "action level" (AL), which is the 8-hour TWA exposure level above which employers must initiate certain compliance activities, such as periodic employee exposure monitoring and medical surveillance. "Excursion limit" (EL) is a term adopted by OSHA specifically for defining a short-term exposure limit for EO. Like a STEL, an EL is the maximum 15-minute exposure to which a worker may be subjected. ACGIH, a private professional organization, recommends "threshold limit values" (TLVs), defined in terms of 8-hour TWAs, 15-minute STELs, and/or ceiling limits, for a large number of chemical substances and physical agents.

Table 3 lists chemical agents found in liquid chemical sterilant/HLD formulations and gaseous chemical sterilization systems and the exposure limits currently mandated by OSHA and recommended by ACGIH. Additional information on OSHA requirements can be found on the OSHA Internet Home Page at http://www.osha.gov. Additional information on ACGIH recommendations can be found in ACGIH (1999).

5.6.3 Material Safety Data Sheets

The MSDS for a chemical used in a liquid chemical sterilant/HLD formulation or gaseous chemical sterilization system provides the user with valuable information about the toxicity of the product as well as other safety information, such as explosion hazards, required safety equipment, and safe exposure limits for individual chemicals. The following information must be included in the MSDS:

a) the identity of the chemical or product;

b) the chemical name and common name of the substance;

c) the chemical name and common name of hazardous ingredients;

d) the physical and chemical characteristics;

e) the physical hazards, including the potential for fire, explosion, and reactivity;

f) the health hazards, including signs and symptoms of exposure;

g) the primary routes of exposure;

h) the OSHA-mandated PEL or the ACGIH-recommended TLV;

i) a statement on whether the chemical is listed as a carcinogen by the National Toxicology Program, the IARC, or OSHA;

j) precautions for safe handling, use, and disposal;

k) generally applicable control measures, including appropriate engineering controls and personal protective equipment;

l) emergency and first-aid procedures;

m) the latest findings in the published literature;

n) date of preparation of the MSDS or date of the most recent revision or update;

o) the name, address and telephone number of the manufacturer.

Annex E provides the form that OSHA suggests (but does not require) be used for an MSDS. Manufacturers may use a different format, but they must provide the same basic information. It is important that users of chemical sterilants/HLDs obtain and understand the contents of the MSDS for the product that they are using. OSHA requires that an MSDS for each hazardous chemical be maintained on site and be readily accessible, during each work shift, to employees when they are in their work areas. Users should be sure to obtain the latest revision of each MSDS, as MSDSs are frequently updated.

5.7 State and local regulations

Many states and local communities have safety, health, and community “right-to-know” regulations applicable to the use and disposal of chemical sterilants. By law, such regulations may not be less stringent than the corresponding federal regulations. In some cases, however, state and local requirements are more stringent than those imposed at the federal level. Health care personnel should know their obligations under state laws and local ordinances.

6 Selection criteria

6.1 General

Various formulations of liquid chemical sterilants and high-level disinfectants are commercially available, and new gaseous chemical sterilization techniques have been developed. This section provides suggestions on the types of questions that users should ask themselves, sterilant/HLD manufacturers, and device manufacturers when choosing sterilizing agents and equipment.

NOTE—Users are cautioned to request manufacturers to substantiate, in written documentation, the answers to all questions that are applicable to the selection process.

6.2 General considerations

a) Has the process been cleared by FDA?

b) When should chemical sterilization or high-level disinfection be selected?

c) What types of medical devices are suitable for sterilization/high-level disinfection by this product or process? What criteria were used to determine the suitability of a device for chemical sterilization or high-level disinfection?

d) How is sterilization/high-level disinfection accomplished? (What is the process, and how is it used?)

e) Is a dedicated container or other equipment needed for use of the liquid chemical sterilant/HLD?

f) How can the efficacy of the product or process be measured? How can the user determine if the product is effective, initially and after several uses? (For example, is there a test to determine the concentration or strength of an active chemical?)

g) If the device is sterilized without packaging, how does one present the device as a sterile end product? Are there post-process handling instructions?

h) If the process is not intended to be used for wrapped items, does the manufacturer have recommendations for transporting sterilized items to the point of use to ensure maintenance of sterility?

i) What are the limitations of the product or process?

j) Before exposing a device to the product or process, how should it be cleaned?

k) If the chemical sterilant is gaseous, is emission control technology required? Is a dedicated exhaust needed?

l) How much time is required for the “complete” sterilization or high-level disinfection process? That is, how much time is needed to ready the liquid chemical sterilant/HLD or gaseous chemical sterilization process and to prepare and process an item so that it is ready for reuse?

m) Will the processed item remain sterile in storage, or must it be used immediately?

n) Will the gaseous chemical sterilant penetrate current types of packaging, including rigid sterilization container systems?

o) Is the system user friendly? For example, how many steps are involved in the process? Do the sterilization/high-level disinfection parameters have to be selected (i.e., time, temperature, concentration)? How much inservice training is required? What is required to ensure operator competency?

p) Is the process compatible with the packaging (if applicable)?

q) Are there any special preparations for the medical device (e.g., deflation of a mouthpiece)?

r) Is control of water quality critical to the process? If so, what water-control steps are necessary?

6.3 Health and safety considerations

a) To what extent has toxicity testing been performed?

b) Has a copy of the MSDS been provided?

c) What are the potential short- and long-term adverse health effects of overexposure to the liquid chemical sterilant/HLD or gaseous chemical sterilant?

d) Is the liquid chemical sterilant/HLD or gaseous chemical sterilant potentially toxic to personnel? In what way? Are there toxic vapors or toxic byproducts? Does the liquid chemical sterilant/HLD or gaseous chemical sterilant react with certain materials (e.g., cleaning agents, adhesives)?

e) At what level of exposure is the liquid chemical sterilant/HLD or gaseous chemical sterilant toxic to humans? By what route of exposure is it toxic (skin contact, inhalation)? Is there an applicable OSHA regulation for occupational exposure?

f) How would the user be able to detect toxicity problems? What are the symptoms of adverse health effects?

g) Is personal protective attire or equipment recommended? Is environmental or personnel monitoring required by OSHA or recommended by ACGIH? If so, which methods are appropriate?

h) Are there specific instructions that explain how toxic conditions or reactions can be avoided during use? For example, must time, temperature, or humidity be controlled? Should a local exhaust hood be used?

i) Are special storage conditions necessary for the liquid chemical sterilant/HLD, gaseous chemical sterilant, or processed items?

j) Does the liquid chemical sterilant/HLD or gaseous chemical sterilant leave residues on processed items that could be toxic to patients or staff members? Is there a method of reducing residues on processed items to nontoxic levels? If it is necessary to aerate processed items, what are the time and temperature parameters? How can adequate aeration be monitored and ensured? If rinsing with sterile water is recommended, how can one ensure that the sterility of items is maintained? What tests have been performed by the manufacturer to document that the recommended rinse process will adequately remove residues?

k) Is contact (allergic) sensitization or tissue irritation a potential health effect?

l) Are there physical hazards such as fire or explosion?

m) Can heat or other environmental conditions cause chemical changes in the liquid chemical sterilant/HLD or gaseous chemical sterilant that would result in other hazards?

n) Will accidental addition of other substances cause hazards?

o) What precautions should be taken in the disposal of the liquid chemical sterilant/HLD? Even if the product is itself nontoxic when discarded, can it react with other substances (in the sewer, for example) to form new volatile or toxic products? Are there applicable federal, state, or local regulations?

p) What level of inservice instruction or other personnel training in the safe use of the liquid chemical sterilant/HLD or gaseous chemical sterilization system does the manufacturer provide?

q) What level of testing has been done to determine that the types of devices sterilized or high-level disinfected by the process remain safe for patient use after repeated processing?

6.4 Effectiveness

a) Are test results available to indicate what types of materials and devices can be sterilized or high-level disinfected without adverse effects on the items? On the patient? On the effectiveness of the liquid chemical sterilant/HLD or gaseous chemical sterilant?

b) What types of materials or devices can and cannot be sterilized or high-level disinfected effectively? Are data available demonstrating the effectiveness of the product in sterilizing or high-level disinfecting specific types of devices? Are there any restrictions on the types of devices that can be sterilized or high-level disinfected (e.g., devices with particular lumen diameters, devices with hinges, devices of specified length)? Is an itemized list available showing the types of devices that were tested?

c) Must items be partially or completely disassembled before exposure to the liquid chemical sterilant/HLD or gaseous chemical sterilization process?

d) Are test results available demonstrating how the presence of organic material, inorganic material, and/or residual detergent affect the effectiveness of the sterilization or high-level disinfection process? Did the manufacturer challenge sterilization using organic and inorganic substances?

e) What are the manufacturer's recommended sterilization or high-level disinfection parameters to ensure effectiveness? For liquid chemical sterilants/HLDs that require dilution, what quality of water (e.g., hard, soft) should be used? At what temperature should the liquid chemical sterilant/HLD be used? How many times, or for what length of time, can it be reused? Is it possible to measure the strength or concentration of the active chemical in the activated solution? Must the test be manufacturer specific, or is there a suitable generic test (e.g., a commercially available test strip)?

NOTE—The liquid chemical sterilants/HLDs cleared by FDA usually have specific chemical indicator strips designed to detect the minimum recommended concentration of the active agent. A generic strip might not be designed to show the color change at the correct minimum recommended concentration.

f) Is the positioning of the device in the liquid chemical sterilant/HLD or gaseous chemical sterilizer critical?

g) What are the manufacturer's recommendations for the packaging that should be used (if applicable)?

h) Are test results available indicating that the effectiveness of the process can be measured or monitored? How can the effectiveness of the process be ensured or documented? Would the user know if the process did not "work"?

i) What are the important factors in the reuse of the liquid chemical sterilant/HLD (e.g., dilution, time, temperature, organic soil, bioburden)?

j) Does the manufacturer of the gaseous chemical sterilizer or liquid chemical sterilant/HLD have data demonstrating microbial kill on and within the devices processed? Were the test organisms inoculated into the areas of the device hardest to be reached by the chemical agent? Were worst-case sterilizing conditions evaluated (e.g., half cycles for gaseous chemical sterilization systems)?

k) Is the manufacturer aware of instances of failure of the liquid chemical sterilant/HLD or gaseous chemical sterilizer, even when the product was properly used according to the manufacturer's directions?

6.5 Materials compatibility

a) What testing has the manufacturer performed to demonstrate the compatibility of the liquid chemical sterilant/HLD or gaseous chemical sterilant with medical device materials? Which materials have been shown to be incompatible?

b) Have the devices listed on the label for use with this product been adequately evaluated for degradation of functionality upon prolonged, repeated use of the liquid chemical sterilant/HLD or gaseous chemical sterilant? Have the device manufacturers evaluated the compatibility of their products with the liquid chemical sterilant/HLD or gaseous chemical sterilant?

c) Will the use of the liquid chemical sterilant/HLD or gaseous chemical sterilant affect the ultimate use-life of the processed items? If so, will all the materials in the device be affected or only certain components? Do devices composed of multiple materials pose more compatibility problems than devices composed of a single material?

d) Are there test data establishing a limit, because of materials compatibility, on the number of times that the liquid chemical sterilant/HLD or gaseous chemical sterilant can be used for certain materials?

e) Does the manufacturer recommend additional inspection to assure device functionality? If so, will special instrumentation be needed to perform inspections or tests?

f) Will residuals of previously used chemicals interfere or react with product materials?

g) Is the process compatible with the packaging?

6.6 Cost effectiveness

a) What are the space requirements for use and storage of the liquid chemical sterilant/HLD or gaseous chemical sterilant?

b) Will special equipment be required? If so, at what cost? How much space will be needed?

c) Does the liquid chemical sterilant/HLD, gaseous chemical sterilant, or associated equipment generate the need for utilities or environmental controls that are not normally found in a health care facility?

d) Will extensive training or retraining of personnel be required? Is special expertise needed to use the sterilization/high-level disinfection system effectively?

e) Are there federal, state, or local regulations concerning disposal of the liquid chemical sterilant/HLD or gaseous chemical sterilant? Do the disposal requirements generate the need for additional equipment or space?

f) Are other suitable liquid chemical sterilants/HLDs or gaseous chemical sterilants available? Are test data available comparing their efficacy? If so, what is the comparative cost? How do their safety and performance characteristics, space and utility requirements, and (if applicable) reuse criteria compare with the product under consideration?

g) What is the total cost per cycle? How was it calculated? What were the underlying assumptions?

h) Will the process affect how devices are currently prepared for sterilization or high-level disinfection? Are there any new, special considerations?

i) How will the process affect the end user (e.g., procedure turnover time, use of consumables, labor, training)?

6.7 Matrix of selection criteria

Table 4 is a matrix of major categories of selection criteria versus types of chemical sterilants. It is provided as a tool to use during the selection process.

Table 4—Selection criteria for chemical sterilants

Selection Criteria	Liquid Chemical Sterilants						Chemical Sterilant Gases			
	Glutaraldehyde		Peracetic acid/ hydrogen peroxide		Hydrogen peroxide		Formaldehyde/ alcohol		Gas plasma	
	Advantages	Limitations	Advantages	Limitations	Advantages	Limitations	Advantages	Limitations	Advantages	Limitations
General considerations										
Health and safety										
Effectiveness										
Materials compatibility										
Cost effectiveness										

7 Guidelines for use

7.1 General

Liquid chemical sterilants/HLDs and gaseous chemical sterilization systems vary in their intended use, mode of action, and potential toxicity. It is essential that users follow exactly the instructions for use provided in the labeling of a liquid chemical sterilant/HLD product or gaseous chemical sterilization system.[3]

Such instructions describe the processing procedures and parameters that have been validated by the manufacturer and explain important safety precautions. In addition, labeling instructions for some products identify specific items that can be effectively sterilized or high-level disinfected and/or items for which the sterilization or high-level disinfection method is not suitable. The use of nonvalidated processing conditions can jeopardize the effectiveness of the chemical sterilization or high-level disinfection process or the performance of the device. For example, a sterilant concentration lower than that recommended by the manufacturer could result in process failures, while a concentration higher than that recommended could damage the item being processed.

Certain general principles apply to the safe and effective use of any liquid chemical sterilant/HLD or gaseous chemical sterilization process.

7.2 Assuring safety

All personnel must be advised of the hazards associated with the chemicals with which they will be working, and they should be thoroughly trained in appropriate safety procedures, both general safety procedures and, where applicable, those that pertain to specific hazards that could be encountered. OSHA requires that Material Safety Data Sheets for all hazardous chemicals be maintained on site and readily accessible during each work shift to employees when they are in their work area(s). Both employee and employer compliance with the OSHA Hazard Communication Standard (29 CFR 1910.1200) must be ensured. In particular, compliance with OSHA Instruction Compliance Directive Enforcement Procedures for Occupational Exposure to Formaldehyde must be enforced.

In general, health care personnel should avoid direct contact with chemical sterilants and high-level disinfectants. When using liquid chemical sterilants/HLDs, personnel should wear protective attire, as appropriate, to prevent skin and/or eye contact; and solutions should always be kept covered to avoid inhalation exposure to the fumes. Liquid chemical sterilants/HLDs should always be used in a well-ventilated area; in some cases, a hood and local exhaust ventilation system will be needed as well (see AAMI, 1996a).

Some chemical sterilants and high-level disinfectants are explosive and/or flammable. Special storage conditions and use precautions are required for such products and must be specified on the MSDS. The use of such chemicals in patient treatment rooms is not recommended. To prevent patient exposure to chemical sterilant or high-level disinfectant residues, any aeration or rinsing procedures specified by the manufacturer must be carefully followed.

[3] Special considerations apply to glutaraldehyde. See annex C.

7.3 Assuring effectiveness

The manufacturer's recommended processing procedures and parameters should be followed. These procedures and parameters are the basis of the manufacturer's FDA-cleared claims.

Thorough cleaning of items is an important first step in any sterilization or high-level disinfection process. The process has been tested against a known number of microorganisms, and its success depends on the cleanliness of the items to be processed. Organic matter such as serum, blood, pus, or fecal material can dilute or inactivate the active ingredient in the liquid or gaseous chemical sterilant or HLD and/or can interfere with its contact with microorganisms remaining on device surfaces. Items should be cleaned until no visible tissue residue or fluid remains on them.

Substances such as soap, detergent, cork, cotton, lint, cotton wool, cellulose sponges, and the minerals found in hard water might also affect the efficacy of the liquid chemical sterilant/HLD or gaseous chemical sterilant. The introduction of detergents, for example—as could occur if the device is inadequately rinsed after cleaning—can alter the pH of a liquid chemical sterilant/HLD solution. Some agents are more effective in killing microorganisms under alkaline conditions; others are more effective under acidic conditions. For some liquid chemical sterilants/HLDs, pH monitoring is advisable, at least during the initial setup and evaluation of the process.

It is also necessary to remove excessive moisture from items. Liquid chemical sterilants/HLDs can be diluted by water remaining on surfaces and in the lumens of items, and the concentration of the active ingredient can be reduced to a level too low to be effective in killing certain microorganisms in the recommended exposure time. If there has been significant dilution of the liquid chemical sterilant/HLD, as revealed by concentration monitoring, the solution should be discarded even if it has not yet reached the manufacturer's recommended reuse time, number of reuses, or expiration date. Some liquid chemical sterilants/HLDs are accompanied by test systems (e.g., test strips) that can and should be used to determine the use-life of the product.

When preparing activated solutions, the user should follow the liquid chemical sterilant/HLD manufacturer's instructions concerning the microbial and/or chemical quality of the water to be used in the formulation. For some liquid chemical sterilants/HLDs, it may be acceptable to use hard water (i.e., tap water); for others, soft or other treated water is needed. If a water treatment process is used, it should be monitored to ensure that the appropriate water quality is achieved.

The user should follow the liquid chemical sterilant/HLD manufacturer's recommendations concerning the type of container (i.e., materials composition) that should be used to prepare the activated solution to ensure that there is no interaction between the container and the active or inert ingredients of the liquid chemical sterilant/HLD. In addition, the container used to store an activated or ready-to-use liquid chemical sterilant/HLD should not interact with its active or inert ingredients.

Containers of liquid chemical sterilants/HLDs should be covered to prevent exposure of personnel to fumes, to avoid evaporation (and thus a change in concentration) of the liquid chemical sterilant/HLD, and to avoid environmental fallout (e.g., lint, dust) into the solution. The concentration of the active ingredients in activated solutions should be monitored at least daily, before and after the day's workload, or according the manufacturer's directions.

Only those liquid chemical sterilants/HLDs labeled for reuse should be reused; the specified use-life, number of reuses, or expiration date must not be exceeded. A reuse claim on the product label indicates that the manufacturer has documented that, after simulated reuse of the liquid chemical sterilant/HLD for the period of time specified, the product remains effective in killing bacterial spores. However, liquid chemical sterilant/HLD solutions should not be used if the concentration of active ingredient falls below the product's minimum recommended concentration (MRC), regardless of the number of days that the solution has been in use.

Annex A
(informative)

Microbial lethality

Both physical sterilization processes (e.g., steam) and chemical sterilization processes are defined by their effectiveness against a range of microorganisms, including bacterial spores, vegetative bacteria, mycobacteria, and viruses. However, the methods used to validate physical sterilization and gaseous chemical sterilization processes differ from those used to validate liquid chemical sterilization processes.

Because bacterial spores have the greatest resistance to most sterilization processes (figure A.1), the effectiveness of a liquid or gaseous chemical sterilant is determined by its ability, under specified conditions, to kill bacterial spores.

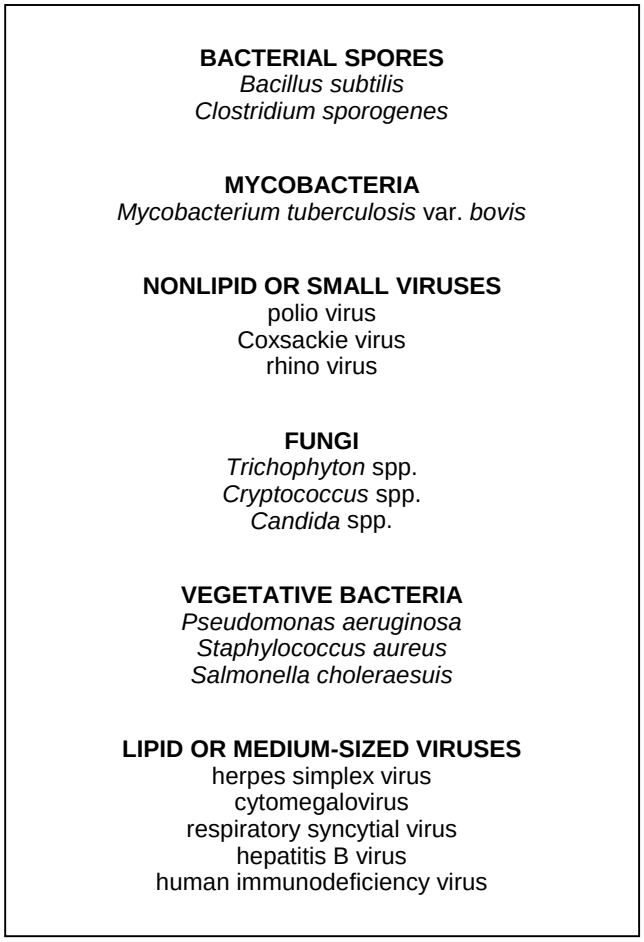


Figure A.1—Descending order of resistance to germicidal chemicals
[Adapted from Block (1991).]

The presence of viable microorganisms can be confirmed by culturing. Current methods of sterilization validation look for viable microorganisms. Thus, the effectiveness of sterilization is measured in terms of the probability of culturing a viable microorganism or of detecting a nonsterile unit. This probability of culturing a viable microorganism or detecting a nonsterile unit is referred to as the sterility assurance level (SAL). In practice, sterilization processes are validated to a SAL of 10^{-6}, i.e., a one-in-a-million chance of recovering a viable microorganism. The SAL concept is based on the ability to extrapolate probabilities of survivors remaining on devices after exposure to a sterilization process. For example, if a sterilization process demonstrated log linear kill kinetics, then the process exposure time

would be determined by linear extrapolation to a log population of 10^{-6} (SAL). Since even traditional sterilization methods, including steam and EO, may not demonstrate complete log linear kinetics, mathematical models are built that yield a conservative calculation of the exposure time necessary for a SAL of 10^{-6} (Block, 1991).

Since constant rates of kill (log linear kinetics) have not been demonstrated for most liquid chemical sterilants, other methods are used to evaluate the efficacy of liquid chemical sterilants. Typically, these methods are qualitative and are based on demonstration of total kill endpoints. Examples of such test methods include the AOAC Sporicidal Test, the AOAC Use-Dilution Test, and the AOAC Fungicidal Test. As the AOAC Sporicidal Test is now performed, the probability of a survivor cannot be accurately estimated. In other words, because the AOAC Sporicidal Test is an endpoint test (total exposure time), it does not permit the accurate calculation of a SAL or a determination of whether log linear kinetics are present. In the absence of constant kill rates, one cannot necessarily predict very low risks of sterilization failures, as with traditional sterilization processes. Therefore, for a device processed by a method validated with endpoint measures alone, the calculated probability that it is sterile would not be known. Tests of liquid chemical sterilants against spores in suspension can be used to obtain quantitative data on the rate of kill. However, spores on device surfaces may provide a different challenge to liquid chemical sterilants than spores in suspension.

Additional technical information on methods used to determine microbial lethality can be found in the bibliography (AOAC, 1995; Beloian and Stuart, 1968; Block, 1991; Cremiux and Fleurette, 1991; Miner, Mulberry, *et al.,* 1995; Pflug and Schmidt, 1968; Stonehill, Krop, and Borick, 1963). For information on FDA regulatory requirements, contact either the Chief, Infection Control Devices Branch (HFZ-480), Center for Devices and Radiological Health, FDA, 9200 Corporate Blvd., Rockville, MD 20850 (301/443-8913); or FDA's Web site at http:www.fda.gov/cdrh/ode/lcgguide.html.

Annex B
(informative)

Materials compatibility of chemical sterilants and high-level disinfectants

B.1 Introduction

An important aspect of the safety and efficacy of a chemical sterilant or HLD is its compatibility with the materials from which medical devices are constructed. Successful use of a chemical sterilant or HLD entails not only the killing of microorganisms but also the retention of the physical integrity and function of the processed device. When selecting a chemical sterilant or HLD, the prospective user should weigh materials compatibility as heavily as efficacy. The chemical interaction of a sterilant or HLD with device materials can adversely affect device safety and effectiveness in various ways. The extent of the reactivity depends on many factors:

a) *The chemical nature of the chemical sterilant or HLD, including inert ingredients:* The mode of microbicidal action of most chemical sterilants and HLDs is either alkylation or oxidation. Alkylating agents (such as glutaraldehyde, formaldehyde, and ethylene oxide), and oxidizing agents (such as hydrogen peroxide and peracetic acid) not only alkylate or oxidize microorganisms and organic matter but also might react with the device materials and alter the physical integrity and function of the device. Variations in the formulation of "inert" ingredients in the chemical sterilant or HLD also might affect materials compatibility. Additives that are considered inert in terms of microbial kill might not be inert in terms of materials compatibility.

b) *The types of polymeric materials or metals involved:* Many types of polymeric materials and metals are used in the manufacture of medical devices (see B.2 and B.3). Some materials are resistant to reaction with chemical sterilants and HLDs, while others undergo reaction but are functionally unaffected by the changes. Some materials, however, undergo chemical reactions that adversely affect the properties and function of the material. Ideally, if a device is heat sensitive, it will be manufactured with materials that are compatible with chemical sterilants and HLDs.

c) *The conditions of use (e.g., chemical sterilant or HLD concentration, temperature, contact time, repeated exposure of the device to the chemical sterilant or HLD):* Chemical changes can be additive, so the conditions of use of a chemical sterilant/HLD can play a role in materials compatibility. In general, for a given chemical sterilant/HLD, the likelihood of chemical attack on materials increases with higher chemical sterilant/HLD concentration, higher temperature, and longer exposure time. Repeated exposure of a device to a chemical sterilant/HLD also might have an impact on materials compatibility. Device manufacturers conduct tests to determine the effects of common chemical sterilants and HLDs on their products under expected use conditions. Therefore, when a chemical sterilant or HLD is used, it is best to follow the instructions of both the chemical sterilant or HLD manufacturer and the device manufacturer to minimize adverse effects.

d) *The internal stresses built into the device by its design and/or manufacture:* Some device designs are more susceptible to damage by a chemical sterilant or HLD than are other types of designs. For example, a device with sharp corners is more likely to fail because of high internal stresses, fatigue, or stress corrosion.

e) *The external stresses on the device (e.g., bending, flexing, twisting, or pressing during use):* Exposure of a device to a critical stress or load combined with exposure to a chemical sterilant or HLD can lead to premature device or component failure. The stresses from repeated use of the device might fatigue the materials so that they show the effects of chemical reaction sooner.

B.2 Effects on polymeric materials

The interaction between chemical sterilants or HLDs and polymers can range from no interaction at all to chemical attack that breaks the chemical bonds of the polymer chain. Incompatibility can manifest itself in crazing (thin streaks appear), cracking, swelling, dissolution, softening, or embrittling. Any one of these changes in the polymer could lead, in time, to poor device performance or even to failure; difficulty in cleaning and/or sterilization/high-level disinfection could also result. Among the types of polymers used in device manufacture are thermosets, thermoplastics, elastomers or rubbers (including thermoplastic elastomers), plastisols, molding compounds, copolymers, and polymer alloys. Applications of these polymers include knobs, housings, and structural parts (e.g., castings and injection moldings), tubing, rods (extrusions), films (blown or extruded), and coatings. Fabricated components frequently are complex systems that contain modifiers such as colorants, antioxidants, lubricants, plasticizers, fillers, and other additives.

These polymer families and systems vary greatly in terms of chemical makeup and reaction with various chemical sterilants and HLDs. While one type of sterilant/HLD might be compatible with a particular polymer, another could attack the polymer. Also, a polymer might be compatible as a heat resin, but the same polymer with additives might be subject to change or deterioration.

While the polymeric material might be able to hold up to the stresses and chemical exposure separately, exposure to both at the same time could cause failure. This phenomenon is known as environmental stress cracking (ESC). Eliminating or decreasing the stress through process modifications such as thermal annealing or changing the type of chemical sterilant or HLD could help to alleviate the problem. The device manufacturer might be able to offer assistance as well.

B.3 Effects on metals

Metals, while not necessarily heat-sensitive, might be exposed to chemical sterilants and HLDs as components of reusable, heat-sensitive devices. Exposure of metals to incompatible solutions can cause chemical and electrochemical attack called corrosion. Stainless steel is the most common type of metal used in the manufacture of reusable medical devices. Liquid solutions, especially those containing chlorides, are of concern for certain stainless steels. Some other nonferrous metals and alloys, including solders, brazes, brasses, Monel® (an alloy of nickel, copper, iron, and manganese), nickel and chrome plating, and anodized aluminum, are also found in certain medical devices and show a variety of effects when exposed to chemical sterilants and HLDs.

B.3.1 Ferrous metals (stainless steels)

The classes of stainless steels and their various alloy compositions demonstrate a wide range of performance properties and corrosion resistance. While relatively impervious to organic solvents, stainless steels can be affected by exposure to certain inorganic solutions and acids. The two classes of stainless steel most commonly used in the medical device industry are austenitic stainless steel, which is known for its superior corrosion resistance, and martensitic stainless steel, which is also called “hardened” stainless steel.

Stainless steel corrosion generally manifests itself as surface blemishes such as roughness and rust. These surface imperfections can lead to difficulties in sterilization or disinfection and can indicate sites at which future device failure could occur. Stainless steels corrode by several different mechanisms, including pitting, crevice corrosion, and stress corrosion cracking (SCC) or hydrogen cracking.

Pitting, caused by exposure to chloride- or bromide-containing solutions, is highly localized corrosion of the steel that results in shallow to deep penetrations. Chloride pitting is the downfall of typically corrosion-resistant austenitic stainless steel. Exposure to a high chloride concentration, elevated temperatures, and stagnant solutions increases the likelihood and severity of pitting. The addition of molybdenum to some stainless steel alloys, such as 316 and 317, enhances the resistance of the material to pitting.

Crevice corrosion occurs in small, shielded crevices such as joint sites, corners, port connections, and gasket areas; it is evident as red rust. These areas are prone to corrosion when devices are immersed in aggressive solutions that are stagnant. Removing stagnant solutions from these crevices decreases the likelihood of crevice corrosion.

Hydrogen cracking and SSC are similar to the ESC phenomenon that occurs in polymeric materials. The corrosion cracks that propagate through stainless steel result from residual or applied stress on the steel in conjunction with exposure to an aqueous corrosive environment. Elevated temperatures increase the amount of corrosion cracking. As with the ESC of polymers, elimination of either the stress or the aqueous corrosive environment alleviates corrosion cracking.

In the early stages of corrosion, the effects on stainless steel are primarily aesthetic. However, if the corrosion is allowed to continue, device failure can eventually occur. Corrosion can also interfere with proper cleaning; consequently, it can inhibit the disinfection or sterilization process. Minimizing the concentration of the corrosive agent, the temperature, and/or the exposure time decreases the likelihood of failure caused by corrosion (but might reduce the effectiveness of the sterilant/HLD).

B.3.2 Nonferrous metals

The compatibility of nonferrous metals with chemical sterilants and HLDs and the resistance of such metals to corrosion depend on the nature of the alloy and the chemical environment. These alloys are more susceptible to corrosion when immersed in strongly acidic solutions than when exposed to a gaseous sterilant. Also, plating and coatings can be affected by chemical attack, even if the plating or coating itself is actually inert. A gap in the film (such as a pinhole, crack, or scratch) exposes a substrate that is subject to corrosion, undercutting, or interfacial attack, which can, in turn, lead to peeling and debonding. Strong oxidizing chemical sterilants and HLDs such as those containing chlorine, hydrogen peroxide, or peracetic acid cause fading of nonferrous metals such as anodized aluminum. Fading of a dyed anodized coating from black or colored to an almost clear color occurs when the organic

dye that is trapped in the anodization layer is bleached. This effect does not typically affect functionality, as the oxide layer remains undamaged, but the dye contained inside the pores in the film is bleached.

B.4 Conclusion

When selecting a chemical sterilant or HLD for use with a particular device, the user should consider not only the possible interactions between the chemical sterilant/HLD and the device materials, but also the conditions of use of the chemical sterilant/HLD. For further information, see AAMI (1994); American Society for Metals (1988); Baijal (1982); Bland, Favero, Oxborrow, *et al.* (1988); Boyer and Gall (1985); Mignot and Arnaud (1994); Plastics Design Library Staff (1994); Sedricks (1979); and Uhlig and Revie (1985).

Annex C
(informative)

Determination of contact times when using glutaraldehyde for high-level disinfection

The scientific community, including regulators, users, and academicians and their organizations, espouse different viewpoints on the testing required and the interpretation of the resulting data in the selection of contact times to be used in device processing with 2% glutaraldehyde solutions. The rationale for each of these viewpoints is summarized in this annex.

NOTE—While the concentration of glutaraldehyde might not be exactly 2% in all formulations, this generic class of products is generally referred to by users as 2% glutaraldehyde.

For determination of high-level disinfection contact times to be included in product labeling, FDA recommends a 10^6 reduction in the number of an appropriate *Mycobacterium* species as an endpoint for high-level disinfection. According to FDA, studies included in 510(k) applications for liquid chemical germicides and automated endoscope reprocessors show that, in many instances, more than 10^5 microorganisms can be recovered from endoscopes after cleaning. The inoculum to be used in simulated-use testing was selected to provide a quantifiable challenge to the germicide being tested, not to represent uncleaned medical devices. The results of such simulated-use testing are the basis for the contact conditions stated in FDA-cleared labeling.

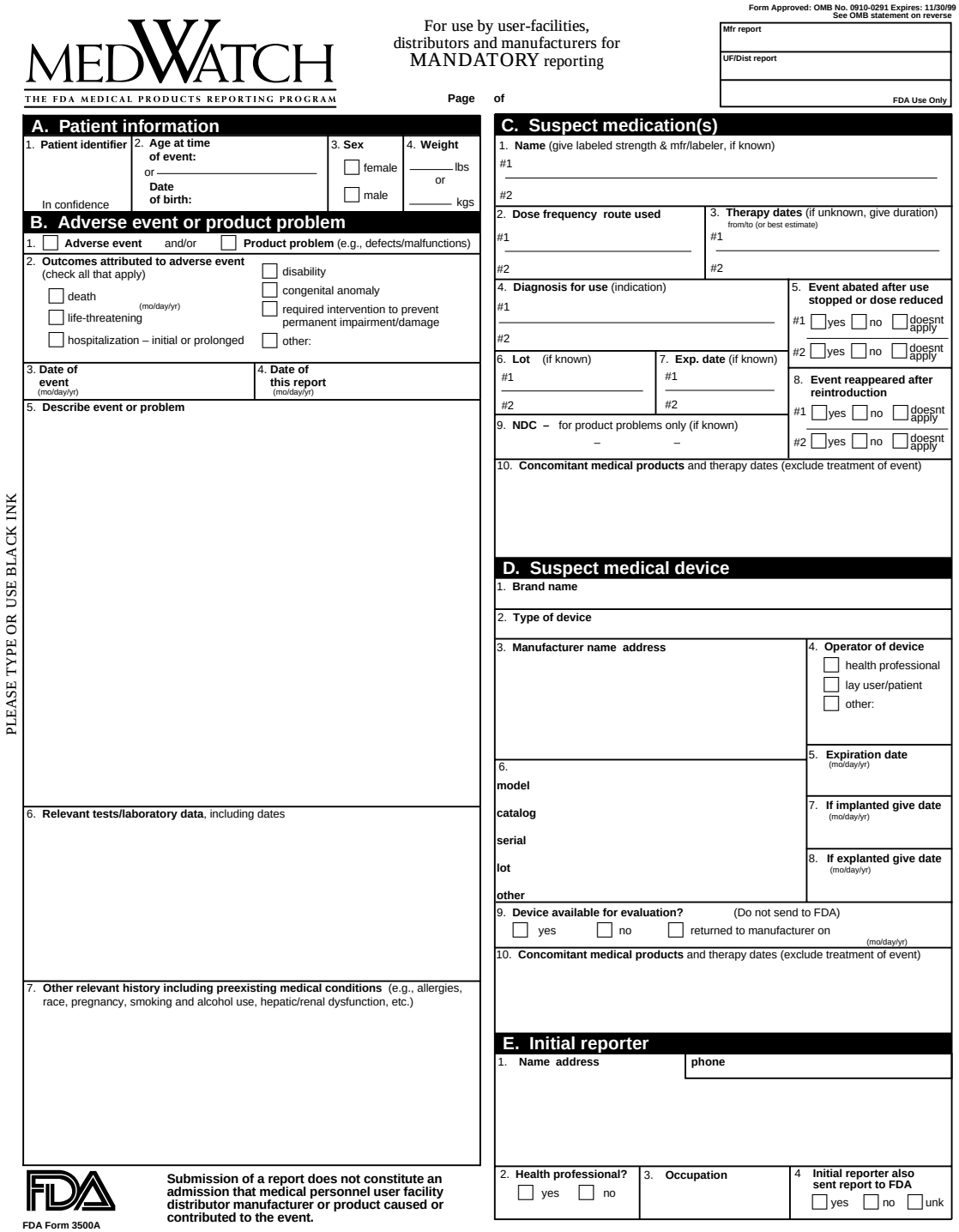
Organizations such as the Association for Professionals in Infection Control and Epidemiology (APIC), the Society of Gastroenterology Nurses and Associates, and the American Society for Gastrointestinal Endoscopy advocate consideration of other data pertaining to microorganism removal during the cleaning process and lethality during disinfection. APIC cites scientific data indicating removal of 4 logs of *M. tuberculosis* during cleaning, followed by the killing of an additional 4 to 6 logs during high-level disinfection for 20 min (Best, 1994; Best, Sattar, Springthorpe, and Kennedy, 1990; Cole, Rutala, Nessen, *et al.,* 1990; Collins, 1986a, 1986b, 1987; Rutala, Cole, Wannamaker, and Weber, 1991a). Based on this information, APIC advocates the use of a • 20-min contact time for high-level disinfection with 2% glutaraldehyde (Rutala, 1996; Rutala, Clontz, Weber, and Hoffman, 1991b). Further justification cited for shorter contact times includes the lack of reports of cross contamination resulting from this regimen. However, this argument is subject to criticism because any infections that do occur might not necessarily be recognized or reported as associated with improperly processed devices.

Both FDA and APIC advocate meticulous cleaning prior to disinfection or sterilization of any patient care item. Proper cleaning removes organic matter, which could interfere with contact between the liquid chemical sterilant/high-level disinfectant and microorganisms remaining on device surfaces, thus reducing the effectiveness of the disinfection process. Glutaraldehyde may cause protein fixation, making patient debris difficult or impossible to remove without damaging the instrument.

In summary, these differing positions have not yet been fully reconciled in the scientific community. It is the responsibility of users to select contact times that are scientifically appropriate for the procedures being conducted in their facilities.

Annex D
(informative)

FDA MedWatch forms for mandatory medical device reporting (MDR) and voluntary reporting by health care professionals



MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For use by user-facilities, distributors and manufacturers for MANDATORY reporting

Form Approved: OMB No. 0910-0291 Expires: 11/30/99
See OMB statement on reverse

Mfr report
UF/Dist report
FDA Use Only

Page of

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. Patient identifier — In confidence
2. Age at time of event: or Date of birth:
3. Sex — female / male
4. Weight — lbs or kgs

B. Adverse event or product problem

1. Adverse event and/or Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - death (mo/day/yr)
   - life-threatening
   - hospitalization – initial or prolonged
   - disability
   - congenital anomaly
   - required intervention to prevent permanent impairment/damage
   - other:
3. Date of event (mo/day/yr)
4. Date of this report (mo/day/yr)
5. Describe event or problem
6. Relevant tests/laboratory data, including dates
7. Other relevant history including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known) #1 #2
2. Dose frequency route used #1 #2
3. Therapy dates (if unknown, give duration) from/to (or best estimate) #1 #2
4. Diagnosis for use (indication) #1 #2
5. Event abated after use stopped or dose reduced #1 yes no doesnt apply #2 yes no doesnt apply
6. Lot (if known) #1 #2
7. Exp. date (if known) #1 #2
8. Event reappeared after reintroduction #1 yes no doesnt apply #2 yes no doesnt apply
9. NDC – for product problems only (if known) – –
10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name
2. Type of device
3. Manufacturer name address
4. Operator of device
   - health professional
   - lay user/patient
   - other:
5. Expiration date (mo/day/yr)
6. model / catalog / serial / lot / other
7. If implanted give date (mo/day/yr)
8. If explanted give date (mo/day/yr)
9. Device available for evaluation? (Do not send to FDA) yes no returned to manufacturer on (mo/day/yr)
10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Initial reporter

1. Name address
   phone
2. Health professional? yes no
3. Occupation
4. Initial reporter also sent report to FDA yes no unk

FDA Form 3500A

Submission of a report does not constitute an admission that medical personnel user facility distributor manufacturer or product caused or contributed to the event.

Medication and Device Experience Report
(continued)

Refer to guidelines for specific instructions

Submission of a report does not constitute an admission that medical personnel user facility distributor manufacturer or product caused or contributed to the event.

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

Page of

FDA Use Only

F. For use by user facility/distributor–devices only

1. **Check one** ☐ user facility ☐ distributor
2. **UF/Dist report number**
3. **User facility or distributor name/address**
4. **Contact person**
5. **Phone Number**
6. **Date user facility or distributor became aware of event** (mo/day/yr)
7. **Type of report** ☐ initial ☐ follow-up #
8. **Date of this report** (mo/day/yr)
9. **Approximate age of device**
10. **Event problem codes** (refer to coding manual) patient code ___ – ___ – ___ device code ___ – ___ – ___
11. **Report sent to FDA?** ☐ yes ☐ no (mo/day/yr)
12. **Location where event occurred** ☐ hospital ☐ home ☐ nursing home ☐ outpatient treatment facility ☐ other: ☐ outpatient diagnostic facility ☐ ambulatory surgical facility
13. **Report sent to manufacturer?** ☐ yes ☐ no (mo/day/yr)
14. **Manufacturer name/address**

G. All manufacturers

1. **Contact office – name/address** (& mfring site for devices)
2. **Phone number**
3. **Report source** (check all that apply) ☐ foreign ☐ study ☐ literature ☐ consumer ☐ health professional ☐ user facility ☐ company representative ☐ distributor ☐ other:
4. **Date received by manufacturer** (mo/day/yr)
5. (A) NDA # IND # PLA # pre-1938 ☐ yes OTC product ☐ yes
6. **If IND protocol**
7. **Type of report** (check all that apply) ☐ 5-day ☐ 15-day ☐ 10-day ☐ periodic ☐ Initial ☐ follow-up #
8. **Adverse event term(s)**
9. **Mfr. report number**

H. Device manufacturers only

1. **Type of reportable event** ☐ death ☐ serious injury ☐ malfunction (see guidelines) ☐ other:
2. **If follow-up what type?** ☐ correction ☐ additional information ☐ response to FDA request ☐ device evaluation
3. **Device evaluated by mfr?** ☐ not returned to mfr. ☐ yes ☐ evaluation summary attached ☐ no (attach page to explain why not) or provide code:
4. **Device manufacture date** (mo/yr)
5. **Labeled for single use?** ☐ yes ☐ no
6. **Evaluation codes** (refer to coding manual) method ___ – ___ – ___ – ___ results ___ – ___ – ___ – ___ conclusions ___ – ___ – ___ – ___
7. **If remedial action initiated check type** ☐ recall ☐ repair ☐ replace ☐ relabeling ☐ other: ☐ notification ☐ inspection ☐ patient monitoring ☐ modification/ adjustment
8. **Usage of device** ☐ initial use of device ☐ reuse ☐ unknown
9. If action reported to FDA under 21 USC 360i(f), list correction/removal reporting number:
10. ☐ **Additional manufacturer narrative** and/or 11. ☐ **Corrected data**

Please DO NOT RETURN this form to this address.

FDA Form 3500A - back

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page of

Form Approved: OMB No. 0910-0291 Expires: 11/30/99
See OMB statement on reverse

FDA Use Only
Triage unit sequence

PLEASE TYPE OR USE BLACK INK

A. Patient information

1. **Patient identifier** In confidence
2. **Age at time of event:** or **Date of birth:**
3. **Sex** ☐ female ☐ male
4. **Weight** ____ lbs or ____ kgs

B. Adverse event or product problem

1. ☐ **Adverse event** and/or ☐ **Product problem** (e.g., defects/malfunctions)
2. **Outcomes attributed to adverse event** (check all that apply)
   - ☐ death (mo/day/yr)
   - ☐ life-threatening
   - ☐ hospitalization – initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. **Date of event** (mo/day/yr)
4. **Date of this report** (mo/day/yr)
5. **Describe event or problem**
6. **Relevant tests/laboratory data** including dates
7. **Other relevant history including preexisting medical conditions** (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. **Name** (give labeled strength & mfr/labeler, if known) #1 #2
2. **Dose frequency route used** #1 #2
3. **Therapy dates** (if unknown, give duration) from/to (or best estimate) #1 #2
4. **Diagnosis for use** (indication) #1 #2
5. **Event abated after use stopped or dose reduced** #1 ☐ yes ☐ no ☐ doesnt apply; #2 ☐ yes ☐ no ☐ doesnt apply
6. **Lot** (if known) #1 #2
7. **Exp. date** (if known) #1 #2
8. **Event reappeared after reintroduction** #1 ☐ yes ☐ no ☐ doesnt apply; #2 ☐ yes ☐ no ☐ doesnt apply
9. **NDC** (for product problems only) – –
10. **Concomitant medical products** and therapy dates (exclude treatment of event)

D. Suspect medical device

1. **Brand name**
2. **Type of device**
3. **Manufacturer name address**
4. **Operator of device**
   - ☐ health professional
   - ☐ lay user/patient
   - ☐ other:
5. **Expiration date** (mo/day/yr)
6. **model** **catalog** **serial** **lot** **other**
7. **If implanted give date** (mo/day/yr)
8. **If explanted give date** (mo/day/yr)
9. **Device available for evaluation?** (Do not send to FDA) ☐ yes ☐ no ☐ returned to manufacturer on (mo/day/yr)
10. **Concomitant medical products** and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. **Name address** **phone**
2. **Health professional?** ☐ yes ☐ no
3. **Occupation**
4. **Also reported to**
   - ☐ manufacturer
   - ☐ user facility
   - ☐ distributor
5. **If you do NOT want your identity disclosed to the manufacturer place an in this box.** ☐

FDA

Mail to: MEDWATCH
5600 Fishers Lane
Rockville MD 20852-9787

or **FA to:**
1-800-FDA-0178

FDA Form 3500

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report experiences with:

- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report product problems – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling
- therapeutic failures

How to report:

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

Important numbers:

- 1-800-FDA-0178 to FA report
- 1-800-FDA-7737 to report by modem
- 1-800-FDA-1088 to report by phone or for more information
- 1-800-822-7967 for a VAERS form for vaccines

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise. However, FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

The public reporting burden for this collection of information has been estimated to average 30 minutes per response including the time for reviewing instructions searching existing data sources gathering and maintaining the data needed and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information including suggestions for reducing this burden to:

DHHS Reports Clearance Office Paperwork Reduction Project (0910-0291) Hubert H. Humphrey Building Room 531-H 200 Independence Avenue S.W. Washington DC 20201

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

FDA Form 3500-back **Please Use Address Provided Below – ust Fold In Thirds Tape and Mail**

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Rockville, MD 20857

Official Business
Penalty for Private Use $300

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES OR APO/FPO

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 946 ROCKVILLE MD

POSTAGE WILL BE PAID BY FOOD AND DRUG ADMINISTRATION

MEDWATCH
The FDA Medical Products Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville MD 20852-9787

Annex E
(informative)

OSHA-recommended format for Material Safety Data Sheets

Material Safety Data Sheet
May be used to comply with
OSHA's Hazard Communication Standard,
29 CFR 1910.1200. Standard must be
consulted for specific requirements

U.S. Department of Labor
Occupational Safety and Health Administration
(Non-Mandatory Form)
Form Approved
OMB No. 1218-0072

IDENTITY *(As Used on Label and List)*	**NOTE: Blank spaces are not permitted. If any item is not applicable or no information is available, the space must be marked to indicate that.**
Section I	
Manufacturer's Name	**Emergency Telephone Number**
Address *(Number, Street, City, State, and ZIP Code)*	**Telephone Number for Information**
	Date Prepared
	Signature of Preparer *(optional)*

Section II – Hazardous Ingredients/Identity Information				
Hazardous Components *(Specific Chemical Identity; Common Names(s))*	**OSHA PEL**	**ACGIH TLV**	**Other Limits Recommended**	**% *(optional)***

Section III – Physical/Chemical Characteristics			
Boiling Point		**Specific Gravity (H_2O = 1)**	
Vapor Pressure (mm Hg)		**Melting Point**	
Vapor Density (AIR = 1)		**Evaporation Rate (Butyl Acetate = 1)**	
Solubility in Water			
Appearance and Color			

Section IV – Fire and Explosion Hazard Data			
Flash Point *(Method Used)*	**Flammable Limits**	**LEL**	**UEL**
Extinguishing Media			
Special Fire Fighting Procedures			
Unusual Fire and Explosion Hazards			

Section V – Reactivity Data			
Stability	**Unstable**		**Conditions to Avoid**
	Stable		
Incompatibility *(Materials to Avoid)*			
Hazardous Decomposition of Byproducts			
Hazardous Polymerization	**May Occur**		**Conditions to Avoid**
	Will Not Occur		

Section VI – Health Hazard Data			
Route(s) of Entry:	**Inhalation?**	**Skin?**	**Ingestion?**
Health Hazards *(Acute and Chronic)*			
Carcinogenicity:	**NTP?**	**IARC Monographs?**	**OSHA Regulated?**
Signs and Symptoms of Exposure			
Medical Conditions Generally Aggravated by Exposure			
Emergency and First Aid Procedures			

Section VII – Precautions for Safe Handling and Use
Steps to Be Taken in Case Material is Released or Spilled
Waste Disposal Method

Precautions to Be Taken in Handling and Storing		
Other Precautions		
Section VIII – Control Measures		
Respiratory Protection *(Specify Type)*		
Ventilation	**Local Exhaust**	**Special**
	Mechanical *(General)*	**Other**
Protective Gloves	**Eye Protection**	
Other Protective Clothing or Equipment		
Work/Hygienic Practices		

Annex F
(informative)

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