cannot be packaged, sterilized, and stored before use. It also is used when there is insufficient time to sterilize an item by the preferred package method. Flash sterilization should not be used for reasons of convenience, as an alternative to purchasing additional instrument sets, or to save time[817]. Because of the potential for serious infections, flash sterilization is not recommended for implantable devices (i.e., devices placed into a surgically or naturally formed cavity of the human body); however, flash sterilization may be unavoidable for some devices (e.g., orthopedic screw, plates). If flash sterilization of an implantable device is unavoidable, recordkeeping (i.e., load identification, patient's name/hospital identifier, and biological indicator result) is essential for epidemiological tracking (e.g., of surgical site infection, tracing results of biological indicators to patients who received the item to document sterility), and for an assessment of the reliability of the sterilization process (e.g., evaluation of biological monitoring records and sterilization maintenance records noting preventive maintenance and repairs with dates).

**Low-Temperature Sterilization Technologies**

Ethylene oxide (ETO) has been widely used as a low-temperature sterilant since the 1950s. It has been the most commonly used process for sterilizing temperature- and moisture-sensitive medical devices and supplies in healthcare institutions in the United States. Two types of ETO sterilizers are available, mixed gas and 100% ETO. Until 1995, ethylene oxide sterilizers combined ETO with a chloroflourocarbon (CFC) stabilizing agent, most commonly in a ratio of 12% ETO mixed with 88% CFC (referred to as 12/88 ETO).

For several reasons, healthcare personnel have been exploring the use of new low-temperature sterilization technologies[825, 851]. First, CFCs were phased out in December 1995 under provisions of the Clean Air Act [852]. CFCs were classified as a Class I substance under the Clean Air Act because of scientific evidence linking them to destruction of the earth's ozone layer. Second, some states (e.g., California, New York, Michigan) require the use of ETO abatement technology to reduce the amount of ETO being released into ambient air from 90 to 99.9% depending on the state. Third, OSHA regulates the acceptable vapor levels of ETO (i.e., 1 ppm averaged over 8 hours) due to concerns that ETO exposure represents an occupational hazard[318]. These constraints have led to the development of alternative technologies for low-temperature sterilization in the healthcare setting.

Alternative technologies to ETO with chlorofluorocarbon that are currently available and cleared by the FDA for medical equipment include 100% ETO; ETO with a different stabilizing gas, such as carbon dioxide or hydrochlorofluorocarbons (HCFC); immersion in peracetic acid; hydrogen peroxide gas plasma; and ozone. Technologies under development for use in healthcare facilities, but not cleared by the FDA, include vaporized hydrogen peroxide, vapor phase peracetic acid, gaseous chlorine dioxide, ionizing radiation, or pulsed light [400, 758, 853]. However, there is no guarantee that these new sterilization technologies will receive FDA clearance for use in healthcare facilities.

These new technologies should be compared against the characteristics of an ideal low-temperature (<60°C) sterilant (Table 9). [851] While it is apparent that all technologies will have limitations (Table 9), understanding the limitations imposed by restrictive device designs (e.g., long, narrow lumens) is critical for proper application of new sterilization technology[854]. For example, the development of increasingly small and complex endoscopes presents a difficult challenge for current sterilization processes. This occurs because microorganisms must be in direct contact with the sterilant for inactivation to occur. Several peer-reviewed scientific publications have data demonstrating concerns about the efficacy of several of the low-temperature sterilization processes (i.e., gas plasma, vaporized hydrogen peroxide, ETO, peracetic acid), particularly when the test organisms are challenged in the presence of serum and salt and a narrow lumen vehicle[469, 721, 825, 855, 856]. Factors shown to affect the efficacy of sterilization are shown in Table 10.

**Ethylene Oxide "Gas" Sterilization**

***Overview.*** ETO is a colorless gas that is flammable and explosive. The four essential

parameters (operational ranges) are: gas concentration (450 to 1200 mg/l); temperature (37 to 63°C); relative humidity (40 to 80%)(water molecules carry ETO to reactive sites); and exposure time (1 to 6 hours). These influence the effectiveness of ETO sterilization[814, 857, 858]. Within certain limitations, an increase in gas concentration and temperature may shorten the time necessary for achieving sterilization.

The main disadvantages associated with ETO are the lengthy cycle time, the cost, and its potential hazards to patients and staff; the main advantage is that it can sterilize heat- or moisture-sensitive medical equipment without deleterious effects on the material used in the medical devices (Table 6). Acute exposure to ETO may result in irritation (e.g., to skin, eyes, gastrointestinal or respiratory tracts) and central nervous system depression[859-862]. Chronic inhalation has been linked to the formation of cataracts, cognitive impairment, neurologic dysfunction, and disabling polyneuropathies[860, 861, 863-866]. Occupational exposure in healthcare facilities has been linked to hematologic changes [867] and an increased risk of spontaneous abortions and various cancers[318, 868-870]. ETO should be considered a known human carcinogen[871].

The basic ETO sterilization cycle consists of five stages (i.e., preconditioning and humidification, gas introduction, exposure, evacuation, and air washes) and takes approximately 2 1/2 hrs excluding aeration time. Mechanical aeration for 8 to 12 hours at 50 to 60°C allows desorption of the toxic ETO residual contained in exposed absorbent materials. Most modern ETO sterilizers combine sterilization and aeration in the same chamber as a continuous process. These ETO models minimize potential ETO exposure during door opening and load transfer to the aerator. Ambient room aeration also will achieve desorption of the toxic ETO but requires 7 days at 20°C. There are no federal regulations for ETO sterilizer emission; however, many states have promulgated emission-control regulations[814].

The use of ETO evolved when few alternatives existed for sterilizing heat- and moisture-sensitive medical devices; however, favorable properties (Table 6) account for its continued widespread use[872]. Two ETO gas mixtures are available to replace ETO-chlorofluorocarbon (CFC) mixtures for large capacity, tank-supplied sterilizers. The ETO-carbon dioxide ($CO_2$) mixture consists of 8.5% ETO and 91.5% $CO_2$. This mixture is less expensive than ETO-hydrochlorofluorocarbons (HCFC), but a disadvantage is the need for pressure vessels rated for steam sterilization, because higher pressures (28-psi gauge) are required. The other mixture, which is a drop-in CFC replacement, is ETO mixed with HCFC. HCFCs are approximately 50-fold less damaging to the earth's ozone layer than are CFCs. The EPA will begin regulation of HCFC in the year 2015 and will terminate production in the year 2030. Two companies provide ETO-HCFC mixtures as drop-in replacement for CFC-12; one mixture consists of 8.6% ETO and 91.4% HCFC, and the other mixture is composed of 10% ETO and 90% HCFC[872]. An alternative to the pressurized mixed gas ETO systems is 100% ETO. The 100% ETO sterilizers using unit-dose cartridges eliminate the need for external tanks.

ETO is absorbed by many materials. For this reason, following sterilization the item must undergo aeration to remove residual ETO. Guidelines have been promulgated regarding allowable ETO limits for devices that depend on how the device is used, how often, and how long in order to pose a minimal risk to patients in normal product use[814].

ETO toxicity has been established in a variety of animals. Exposure to ETO can cause eye pain, sore throat, difficulty breathing and blurred vision. Exposure can also cause dizziness, nausea, headache, convulsions, blisters and vomiting and coughing[873]. In a variety of *in vitro* and animal studies, ETO has been demonstrated to be carcinogenic. ETO has been linked to spontaneous abortion, genetic damage, nerve damage, peripheral paralysis, muscle weakness, and impaired thinking and memory[873]. Occupational exposure in healthcare facilities has been linked to an increased risk of spontaneous abortions and various cancers[318]. Injuries (e.g., tissue burns) to patients have been associated with ETO residues in implants used in surgical procedures[874]. Residual ETO in capillary flow dialysis membranes has been shown to be neurotoxic in vitro[875]. OSHA has established a PEL of 1 ppm airborne ETO in the workplace, expressed as a TWA for an 8-hour work shift in a 40-hour work week. The "action level" for ETO is 0.5 ppm, expressed as an 8-hour TWA, and the short-term excursion limit is 5 ppm, expressed as

a 15-minute TWA[814]. For details of the requirements in OSHA's ETO standard for occupational exposures, see Title 29 of the Code of Federal Regulations (CFR) Part 1910.1047[873]. Several personnel monitoring methods (e.g., charcoal tubes and passive sampling devices) are in use[814]. OSHA has established a PEL of 5 ppm for ethylene chlorohydrin (a toxic by-product of ETO) in the workplace[876]. Additional information regarding use of ETO in health care facilities is available from NIOSH.

***Mode of Action.*** The microbicidal activity of ETO is considered to be the result of alkylation of protein, DNA, and RNA. Alkylation, or the replacement of a hydrogen atom with an alkyl group, within cells prevents normal cellular metabolism and replication[877].

***Microbicidal Activity.*** The excellent microbicidal activity of ETO has been demonstrated in several studies [469, 721, 722, 856, 878, 879] and summarized in published reports[877]. ETO inactivates all microorganisms although bacterial spores (especially *B. atrophaeus*) are more resistant than other microorganisms. For this reason *B. atrophaeus* is the recommended biological indicator.

Like all sterilization processes, the effectiveness of ETO sterilization can be altered by lumen length, lumen diameter, inorganic salts, and organic materials[469, 721, 722, 855, 856, 879]. For example, although ETO is not used commonly for reprocessing endoscopes[28], several studies have shown failure of ETO in inactivating contaminating spores in endoscope channels [855]or lumen test units [469, 721, 879] and residual ETO levels averaging 66.2 ppm even after the standard degassing time[456]. Failure of ETO also has been observed when dental handpieces were contaminated with *Streptococcus mutans* and exposed to ETO[880]. It is recommended that dental handpieces be steam sterilized.

***Uses.*** ETO is used in healthcare facilities to sterilize critical items (and sometimes semicritical items) that are moisture or heat sensitive and cannot be sterilized by steam sterilization.

**Hydrogen Peroxide Gas Plasma**

***Overview.*** New sterilization technology based on plasma was patented in 1987 and marketed in the United States in 1993. Gas plasmas have been referred to as the fourth state of matter (i.e., liquids, solids, gases, and gas plasmas). Gas plasmas are generated in an enclosed chamber under deep vacuum using radio frequency or microwave energy to excite the gas molecules and produce charged particles, many of which are in the form of free radicals. A free radical is an atom with an unpaired electron and is a highly reactive species. The proposed mechanism of action of this device is the production of free radicals within a plasma field that are capable of interacting with essential cell components (e.g., enzymes, nucleic acids) and thereby disrupt the metabolism of microorganisms. The type of seed gas used and the depth of the vacuum are two important variables that can determine the effectiveness of this process.

In the late 1980s the first hydrogen peroxide gas plasma system for sterilization of medical and surgical devices was field-tested. According to the manufacturer, the sterilization chamber is evacuated and hydrogen peroxide solution is injected from a cassette and is vaporized in the sterilization chamber to a concentration of 6 mg/l. The hydrogen peroxide vapor diffuses through the chamber (50 minutes), exposes all surfaces of the load to the sterilant, and initiates the inactivation of microorganisms. An electrical field created by a radio frequency is applied to the chamber to create a gas plasma. Microbicidal free radicals (e.g., hydroxyl and hydroperoxyl) are generated in the plasma. The excess gas is removed and in the final stage (i.e., vent) of the process the sterilization chamber is returned to atmospheric pressure by introduction of high-efficiency filtered air. The by-products of the cycle (e.g., water vapor, oxygen) are nontoxic and eliminate the need for aeration. Thus, the sterilized materials can be handled safely, either for immediate use or storage. The process operates in the range of 37-44$^{o}$C and has a cycle time of 75 minutes. If any moisture is present on the objects the vacuum will not be achieved and the cycle aborts[856, 881-883].

A newer version of the unit improves sterilizer efficacy by using two cycles with a hydrogen

peroxide diffusion stage and a plasma stage per sterilization cycle. This revision, which is achieved by a software modification, reduces total processing time from 73 to 52 minutes. The manufacturer believes that the enhanced activity obtained with this system is due in part to the pressure changes that occur during the injection and diffusion phases of the process and to the fact that the process consists of two equal and consecutive half cycles, each with a separate injection of hydrogen peroxide. [856, 884, 885] This system and a smaller version [400, 882] have received FDA 510[k] clearance with limited application for sterilization of medical devices (Table 6). The biological indicator used with this system is *Bacillus atrophaeus* spores[851]. The newest version of the unit, which employs a new vaporization system that removes most of the water from the hydrogen peroxide, has a cycle time from 28-38 minutes (see manufacturer's literature for device dimension restrictions).

Penetration of hydrogen peroxide vapor into long or narrow lumens has been addressed outside the United States by the use of a diffusion enhancer. This is a small, breakable glass ampoule of concentrated hydrogen peroxide (50%) with an elastic connector that is inserted into the device lumen and crushed immediately before sterilization[470, 885]. The diffusion enhancer has been shown to sterilize bronchoscopes contaminated with *Mycobacteria tuberculosis*[886]. At the present time, the diffusion enhancer is not FDA cleared.

Another gas plasma system, which differs from the above in several important ways, including the use of peracetic acid-acetic acid-hydrogen peroxide vapor, was removed from the marketplace because of reports of corneal destruction to patients when ophthalmic surgery instruments had been processed in the sterilizer[887, 888]. In this investigation, exposure of potentially wet ophthalmologic surgical instruments with small bores and brass components to the plasma gas led to degradation of the brass to copper and zinc[888, 889]. The experimenters showed that when rabbit eyes were exposed to the rinsates of the gas plasma-sterilized instruments, corneal decompensation was documented. This toxicity is highly unlikely with the hydrogen peroxide gas plasma process since a toxic, soluble form of copper would not form (LA Feldman, written communication, April 1998).

***Mode of Action.*** This process inactivates microorganisms primarily by the combined use of hydrogen peroxide gas and the generation of free radicals (hydroxyl and hydroproxyl free radicals) during the plasma phase of the cycle.

***Microbicidal Activity*.** This process has the ability to inactivate a broad range of microorganisms, including resistant bacterial spores. Studies have been conducted against vegetative bacteria (including mycobacteria), yeasts, fungi, viruses, and bacterial spores[469, 721, 856, 881-883, 890-893]. Like all sterilization processes, the effectiveness can be altered by lumen length, lumen diameter, inorganic salts, and organic materials[469, 721, 855, 856, 890, 891, 893].

***Uses.*** Materials and devices that cannot tolerate high temperatures and humidity, such as some plastics, electrical devices, and corrosion-susceptible metal alloys, can be sterilized by hydrogen peroxide gas plasma. This method has been compatible with most (>95%) medical devices and materials tested[884, 894, 895].

**Peracetic Acid Sterilization**

***Overview.*** Peracetic acid is a highly biocidal oxidizer that maintains its efficacy in the presence of organic soil. Peracetic acid removes surface contaminants (primarily protein) on endoscopic tubing[711, 717]. An automated machine using peracetic acid to sterilize medical, surgical, and dental instruments chemically (e.g., endoscopes, arthroscopes) was introduced in 1988. This microprocessor-controlled, low-temperature sterilization method is commonly used in the United States[107]. The sterilant, 35% peracetic acid, and an anticorrosive agent are supplied in a single-dose container. The container is punctured at the time of use, immediately prior to closing the lid and initiating the cycle. The concentrated peracetic acid is diluted to 0.2% with filtered water (0.2 $\mu$m) at a temperature of approximately 50$^{o}$C. The diluted peracetic acid is circulated within the chamber of the machine and