

FDA Executive Summary

Prepared for the November 6 - 7, 2019 meeting of the
General Hospital and Personal Use Devices Panel of the
Medical Devices Advisory Committee

**Reduction of Ethylene Oxide Sterilization Emissions for Medical
Devices and Potential for Utilizing Other Sterilization Modalities**

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I. Overview

Medical devices provided to users and patients as sterile are terminally sterilized using a variety of chemical or physical methods. Ethylene oxide (EtO) sterilization is compatible with a broad range of medical devices and medical device materials and therefore is widely used by medical device manufacturers and contract sterilizers worldwide. During industrial EtO sterilization, large numbers of unsterile medical devices can be sterilized by exposure to EtO gas in a single sterilization chamber at controlled pressure, temperature, and humidity. Roughly half of all sterile medical devices used in the United States (U.S.) are sterilized with EtO in this manner.^{2, 3, 4}

The United States Environmental Protection Agency (U.S. EPA) Fact Sheet for EtO emissions states long term exposure to elevated EtO levels in air (concentrations above an acceptable limit) can cause irritation to the eyes, skin, nose, throat, and lungs, and may increase the risk of some cancers.¹ On February 15, 2019, the Illinois State Environmental Protection Agency (Illinois EPA) shut down the Sterigenics Willowbrook contract sterilizer operation with a seal order regarding concerns about the facility's EtO emissions. The Sterigenics Willowbrook facility provided EtO sterilization services to over 100 medical device manufacturers and sterilized more than 500 types of medical devices. The loss of medical device sterilization capacity at even one facility creates a potential risk for medical device shortages due, in part, to the limited capacity of other sterilization facilities to assume sterilization of the medical devices that were sterilized at a closed facility. In general, contract sterilization facilities run continually with few breaks, at their maximum capacity. Immediately after and since the Willowbrook facility shutdown, the U.S. Food and Drug Administration (FDA) Center for Devices and Radiological Health (CDRH) has worked proactively to mitigate adverse patient impact from the closure by communicating with industry, assessing medical device shortages, interacting with other contract EtO sterilizers, and engaging external experts on potential methods for reducing EtO emissions and identification of alternative sterilization modalities.

The issue of industrial use of EtO to sterilize medical devices and the resultant environmental emissions extends far beyond the seal order for the Willowbrook facility. Actions that affect the industrial use of EtO and the national EtO sterilization capacity for medical devices may have far-reaching implications for public health due to resulting device shortages. EtO is used to sterilize a wide range of medical devices used to protect and promote public health. The types of devices that are sterilized with EtO range from devices used in general healthcare practices (e.g., wound dressings, surgical kits, etc.), more specialized devices used to treat specific areas of the body (e.g., stents, orthopedic implants, etc.), and life sustaining and supporting devices (e.g., pacemakers, heart valves, dialysis sets, etc.). For many medical devices, EtO sterilization may be the only effective sterilization method that does not negatively impact the device or the function of the device. EtO is likely to be used to sterilize medical devices made from certain polymers (plastic or resin), metals, or glass, or those having multiple layers of packaging or hard-to-reach places (e.g., catheters). Using an industrial EtO sterilization process, a shipping container-sized load of medical devices (or more) can be sterilized at the same time. A significant loss of sterilization capacity for medical devices can lead to shortages of medical devices and can pose a threat to public health by delaying or disrupting critical care for patients.

The purpose of this Medical Devices Advisory Committee meeting is to obtain the panel's expert advice on how to address challenges associated with EtO emissions in the environment from medical device sterilization without compromising the assurance of sterility or effective processing of medical devices. The Panel will be asked to consider and recommend:

- Potential strategies for modifying existing EtO use to reduce emissions
- Feasibility of leveraging existing, non-EtO industrial sterilization infrastructure and other sterilization modalities to replace EtO sterilization, and
- Feedback on any actions FDA may be able to take to facilitate reduction of EtO emissions.

In addition to this Advisory Committee meeting, FDA is actively working with sterilization experts, medical device manufacturers, and other government agencies to advance innovative ways to sterilize medical devices with lower levels of currently used agents, and employing new agents or alternatives, while maintaining device safety and effectiveness. Examples of these activities are our ongoing sterilization innovation challenges, which were released this summer. Challenge 1 is aimed at identifying new sterilization methods and technologies and Challenge 2 is aimed at reducing ethylene oxide emissions from existing processes while still ensuring that devices can be effectively sterilized.

II. FDA's Role in Assessing Medical Device Sterility

FDA review of sterilization information in a medical device submission

Medical devices are classified based on the risk the device poses to the patient. Devices are classified into one of three regulatory classes (Class I, II, and III) based on the device's risk and the level of regulatory control necessary to assure the safety and effectiveness of the device. Class I devices, the lowest risk, are subject to the statute's general controls such as labeling and adverse event reporting; and most are exempt from FDA review prior to introduction to the market. Class II devices, intermediate risk, are subject to the general controls and Special Controls tailored to that device type; and most are reviewed by FDA prior to market introduction under the premarket notification or "510(k)" pathway. Class III devices, the highest risk, require Premarket Approval (PMA) prior to marketing and may be subject to postmarket conditions of approval. Generally, FDA reviews device information to determine that there is a reasonable assurance of safety and effectiveness before a device enters interstate commerce in the U.S.

Ensuring device sterilization is an important part of the FDA's assessment of a device's safety profile. The sterilization validation documentation required to clear a device in a 510(k) submission can differ from that submitted in a PMA application for devices labeled as "Sterile" using industrial terminal sterilization processes. For Class III devices, the FDA reviews complete sterilization validations as part of manufacturing controls to assure safety and effectiveness of the medical product in a PMA. However, for Class I and II devices that are subject to clearance under a 510(k), the FDA does not review the complete sterilization validations for all sterilization modalities, but assesses sterility based on the recommendations in the FDA's Sterility Guidance document, *Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile*.

The FDA regulation of EtO sterilization (and all industrial sterilization modalities) for a sterile device submitted under a 510(k) is limited to the effectiveness of the sterilization process for a specific medical device. This assessment includes the use of voluntary consensus standards to ensure that manufacturers of sterile medical devices are utilizing a sterilization process that achieves an acceptable sterility assurance level and to ensure that sterilization does not negatively impact material compatibility and biocompatibility of the devices under review. For example, the American National Standards Institute/ Association for the Advancement of Medical Instrumentation/International Organization for Standardization (ANSI/AAMI/ISO) 10993-7 standard specifies allowable EtO residual limits on medical devices to ensure biocompatibility of the device.

The FDA Sterility Guidance cited above provides examples of some of the sterility information assessed as part of a 510(k) review.⁷ Sterilization process information evaluated in premarket 510(k) submissions may include:

- A description of the sterilization method
- The amount of residual sterilant that remains on the device, if applicable (as part of a biocompatibility assessment)
- A description of the sterilization validation method, including the use of consensus standards, as applicable
- Information supporting a measurable assurance of sterility from the sterilization process for the specific device
- An assessment of the amount of bacterial endotoxin present on the sterilized device and potential for material mediated pyrogenicity
- A description of the sterile barrier system (packaging) for the device and how the packaging maintains a sterile barrier over the proposed shelf life

FDA's review is focused on the medical device, namely its sterility and the process that achieves medical device sterility, (e.g., EtO sterilization). The U.S. EPA reviews and enforces the Clean Air Act regulations for sterilization facilities that emit EtO by assessing EtO emissions from the facilities to ensure they are controlling the emissions and protecting the public from significant risk of EtO exposure.¹ The U.S. EPA considers all sources of EtO emissions. EtO emission sources in addition to medical device sterilization facilities include organic chemical manufacturing, hospital ethylene oxide sterilizers in healthcare facilities, polyether polyols production facilities, and synthetic organic chemical manufacturing facilities.

This distinction between the FDA and the U.S. EPA roles is important for understanding the limits of the FDA's regulatory authority with respect to industrial sterilization: The FDA reviews the medical device output of the sterilization process to ensure medical devices are sterilized using a validated, effective, and repeatable process. The FDA does not have the authority to regulate emissions to the environment from industrial sterilization processes. Also, the FDA does not specify what type of sterilization should be used to sterilize a medical device; the medical device's manufacturer chooses and validates a method and process that will ensure the sterility of the device.

FDA review of hospital sterilizers as medical devices

Another important regulatory distinction is the difference between FDA’s evaluation of industrial sterilizers and its evaluation of hospital or healthcare sterilizers. Healthcare sterilizers are medical devices and industrial sterilizers are not. Industrial sterilization of medical devices is a terminal process implemented as part of medical device manufacturing for devices that are provided to customers as sterile devices. These processes are almost always high-throughput with the capacity to sterilize many medical devices at the same time. The FDA reviews the outcome of these processes (process validation), but it does not regulate the industrial sterilizers themselves. In contrast, hospital or healthcare-based sterilizers are predominantly used to reprocess reusable medical devices for additional uses. Hospital sterilizers generally have smaller chamber sizes and have significantly less capacity for a single application of a sterilization process. For example, hospital steam sterilizers (autoclaves) may be the size of a cabinet or may be a small, table-top unit. FDA reviews hospital sterilizers and their performance as Class II devices under a 510(k) submitted by a sponsor. They are distinct from industrial sterilizers and have different technical considerations and requirements.

When reviewing premarket submissions for hospital sterilizers, FDA considers aspects of the sterilizer such as the software and cybersecurity, its engineering and construction, and the stability of consumable chemical sterilants, as well as, microbicidal performance testing. Table 1 below compares industrial and hospital sterilizers.

Table 1: Comparison of industrial and hospital sterilizers

	Industrial Sterilizers	Hospital Sterilizers
Regulatory Status	Not an FDA regulated medical device	FDA regulated medical devices
Desired Process Outcome	Terminally sterilized, packaged medical devices to be introduced into the supply chain	Last step of on-site reprocessing of reusable medical devices prior to reuse of the device in a healthcare setting or sterilization at point-of-care before device use (e.g., some implants)
FDA Review	FDA reviews the output of the process to ensure effective sterilization of medical devices using a validated process	FDA conducts a detailed review of the safety and effectiveness of the sterilizer including relevant performance and technical characteristics
Sterilization Chamber Sizes	Large; often the size of a large room and can sterilize container-truck-sized loads of medical devices at the same time	Smaller; may be the size of a cabinet or a table-top unit

The distinction between FDA regulation of hospital sterilizers and FDA regulation of industrial sterilizers and industrial sterilization processes is important in the context of this Advisory Committee Meeting because hospital sterilizers, including those using EtO, are not the focus of the discussion on industrial sterilization.

III. Medical device supply chain and shortages resulting from lost EtO sterilizing capacity

Medical Device Supply Chain: Shortage Considerations and Potential Impact on Patient Care

FDA understands that a strong medical supply chain is important to ensuring patients continue to have access to the critical devices and medical procedures they need to sustain and support life. As such, medical device shortages are a serious public health issue that can impact patient lives; and that impact is even more substantial for vulnerable populations such as pediatrics, since they have a limited number of devices and device sources that they can choose from. Until there are effective alternatives, patients will lose access to important devices if EtO is not available at all.

The capacity of EtO sterilization for medical devices in the U.S. is fixed and contract manufacturers are often operating at their maximum throughput. Therefore, it is FDA's understanding that there is not additional capacity for other contract sterilizers to absorb the load for sterilizing products if other sterilization facilities shut down

Irrespective of where the devices are sterilized -- at the manufacturing site, hospital, or at a contract sterilizer -- the sterilization method used for a given product must be validated by appropriate testing to ensure that the process results in adequate device sterilization. To sterilize a device at another sterilization facility is not simply a matter of identifying a site that has capacity (which, as previously stated, is extremely difficult). Other critical and rate-limiting factors should be considered including but not limited to:

- The more products that a firm would need to transfer, the more time it would take to switch those products and re-validate each one at the new site.
- Even for one product, validation testing could take several months.
- Because of just-in-time device production -- which serves the existing healthcare delivery model of just-in-time ordering as hospitals and other care facilities do not have space to maintain product inventory -- long gaps in manufacturer access to terminal sterilization would likely result in temporary, spot or even national shortages with an increase in backorders.

A change, if feasible, in the sterilization modality-- e.g., from EtO to radiation -- also requires extensive validation testing and is subject to the same rate-limiting factors as above.

The downstream implications of potential medical device shortages because of a lack of sterilization capacity has consequences for hospitals and ultimately patient care. On February 15, 2019, the Illinois EPA issued a seal order to stop the Sterigenics facility in Willowbrook, IL ("Willowbrook"), from sterilizing medical products with EtO. Following the seal order, the FDA proactively reached out to group purchasing organizations (comprised of hospitals and hospital systems of various sizes) who mobilized efforts to understand whether products used by their hospitals were impacted and if so to what extent. They sent out regular communications to their members regarding supplier status, available alternatives, and potential shortage concerns. As part of alternative approaches to ensure patients had access to the devices they needed, hospitals even considered obtaining non-sterile product and sterilizing it onsite at the hospital. This raised concerns about workflow impacts and final product sterility since these activities were not a part of standard processes. Hospitals also used alternative devices to those that they were unable to procure because of a lack of sterilization capacity. While these alternatives had similar functionality, clinical

workflows may have been affected because of the learning curve associated with clinicians becoming familiar with this device.

Group purchasing organizations, individual hospitals, and the public at large were encouraged to report shortage concerns to the FDA. Such voluntary reporting is particularly important since FDA does not have authority to require device manufacturers to report potential device shortages to us.

FDA currently uses various tools and resources to mitigate shortage situations, and their application to the availability of EtO sterilization is described in the following section.

FDA's response to EtO contract sterilizer closure

Upon learning of the Willowbrook seal order, FDA immediately responded by coordinating data requests, monitoring the developing situation, participating in internal and public communications, and working with manufacturers to mitigate any medical device shortages.

Identifying devices at risk for shortage:

FDA searched its databases for devices listed as being sterilized at the Willowbrook facility. Simultaneously, it requested a list of devices sterilized at the Willowbrook facility from Sterigenics management and cross-referenced that list with known information. In total, FDA found that Sterigenics Willowbrook sterilized 510 types of medical devices, manufactured by more than 120 firms.

After generating the list of devices, FDA determined which devices might be at risk of shortage. The review identified four devices, three ophthalmic devices and one cardiac device, manufactured by either a single firm or only a few firms, and/or that are used for life-saving or life-preserving procedures. FDA promptly contacted the manufacturers of those devices to determine if they had device shortage concerns. The only shortage threat appeared to be for the cardiac device, which the firm had in limited stock. Prior to the Willowbrook closure, the firm had submitted a request for approval to move device sterilization to a different location. FDA prioritized the request and approved it within 3 weeks, which avoided a shortage.

Coincident with these efforts, several external, independent sources made FDA aware of another product, a tracheostomy tube, that became in short supply. FDA had originally deemed this device not at risk of shortage because of readily available alternative devices; however, further investigation revealed unique device characteristics making the device essential for the pediatric subpopulation of patients.

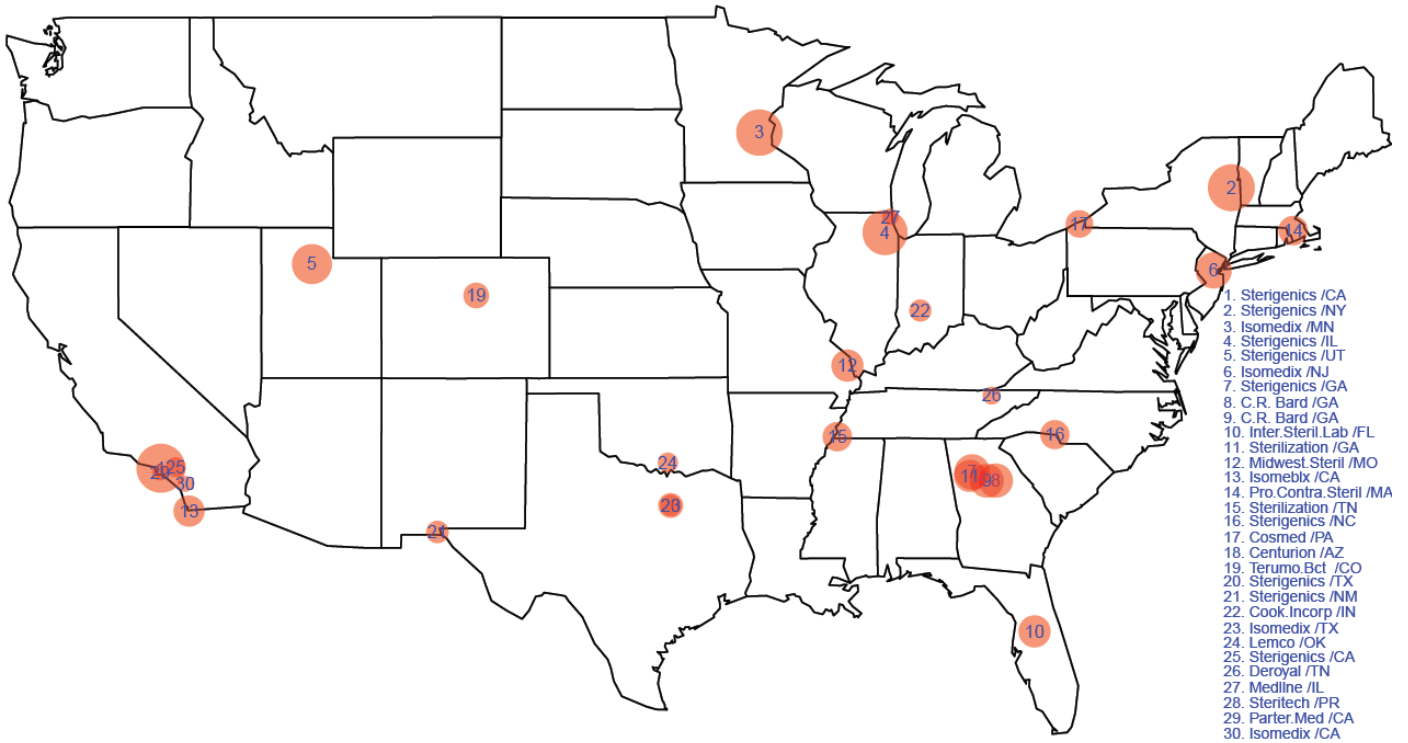
FDA reached out to the remaining firms to complete a survey of the affected landscape. None of the firms reported supply problems during the initial weeks after the Willowbrook closure. However, over the next month or two, 6 additional firms reported impending supply depletions to FDA.

Identifying devices that may have acceptable alternative methods of sterilization:

For all devices determined to be at risk of shortage, every manufacturer's device shortage mitigation plan involved either changing the EtO sterilization site to another location or distributing other unaffected devices to users as replacements for the ones in shortage. No shortage mitigation plan employed the use of an alternative method of sterilization. Thus, in many cases, shortage mitigation plans proved effective for only a few weeks because low stock reserves combined with high device utilization rates quickly exhausted available sterile product. This was compounded by the inability to completely implement some of the

mitigation plans because of the sudden, high demand placed on the limited number of remaining EtO sterilization facilities, which, even before the closure, were functioning at or near capacity.

Figure 1: U.S. EtO contract sterilizers (Top 30 based on registration and listing numbers)



FDA asked the manufacturers of the tracheostomy tube discussed above whether they could use alternative sterilization methods to mitigate a shortage. The manufacturers cited technical problems (e.g., incompatibility between device materials and process methods) and/or business considerations (e.g., increased costs associated with the other method and/or transportation) that prevented the use of other sterilization methods.

Outreach to the public and device manufacturers:

The FDA initiated further outreach on March 26, 2019, with dissemination of wide public messaging through its website.⁹ FDA engaged and maintained contact with several group purchasing organizations and medical professional societies to help detect problems to device access by healthcare facilities as quickly as possible and to provide timely situation updates. Through these collaborations, FDA was able to quickly detect, evaluate, mitigate, and in some cases, prevent additional shortages.

Summary:

Of the more than 2 million medical devices listed in the Global Universal Device Identification Database (GUDID), 40% are provided as sterile to users and patients. The literature shows about 50% of those devices

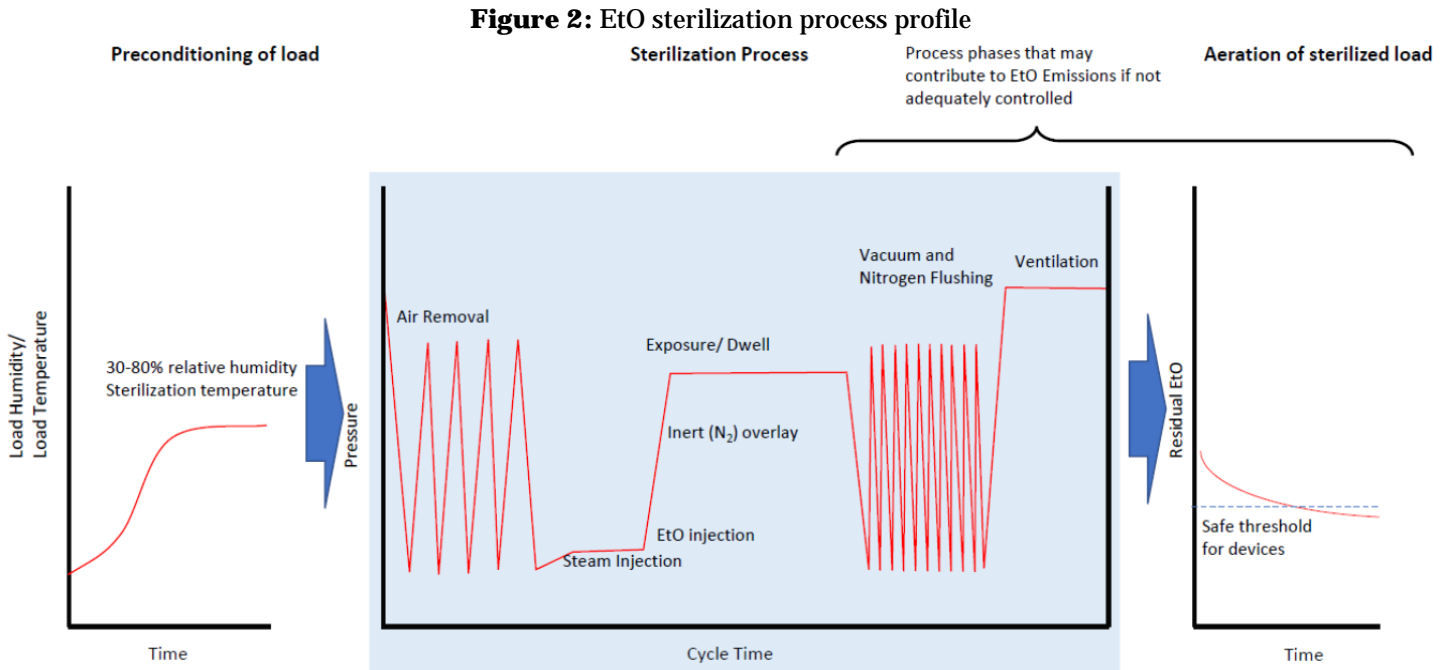
are sterilized with EtO,²⁻⁴ ranging from 510(k)-exempt devices used in general healthcare practices (e.g., wound dressings) to more specialized, high-risk devices used to treat specific areas of the body (e.g., vascular stents) and life-saving or life-sustaining medical devices (pacemakers, heart valves, dialysis sets, etc.).

Industrial EtO sterilization has a high throughput capacity, broad material compatibility, low cost, and effective bactericidal, sporicidal, and viricidal activity; therefore, it is used to sterilize a large number and variety of medical devices.¹⁰

These beneficial properties of EtO sterilization have significantly contributed to the design, advancement, and evolution of delicate, complex, and more sophisticated medical devices that enhance healthcare in the U.S and reliance on its use in the U.S. for sterilization of medical devices. In other words, without EtO sterilization, at least 20% of all medical devices, and 50% of those sterilized, would be at risk of being no longer available to patients and users. Not only would this have a serious impact on public health, but because all implantable devices and invasive procedures rely on product sterility, the sickest patients would be most at risk.

IV. EtO Sterilization of Medical Devices

Overview of an EtO sterilization process



Preconditioning of Load - Devices are prepared for sterilization using environmental controls for temperature and relative humidity for predefined conditions because the EtO sterilization process requires that the sterilization load contains moisture. This process may take hours to days to complete.

Air Removal - A vacuum is created in the sterilization chamber by pulling a deep vacuum or by a series of partial vacuums followed by nitrogen injections (as shown in Figure 2 above). The method used depends upon the items being sterilized (including packaging). Some packaging may burst under vacuum if a deep vacuum is created in a single step.

Steam Injection – Moisture is an important component of an EtO sterilization process but may be lost during the air removal phase. Steam is injected into the sterilization chamber after air removal to ensure the sterilization load maintains the right humidity.

EtO Injection – Gaseous ethylene oxide is injected into the chamber.

Inert Gas (N₂) Overlay – In some EtO sterilization processes, an inert gas like diatomic nitrogen is injected into the chamber after the EtO injection to create top pressure which pushes the EtO gas into the sterilization load.

Exposure/Dwell - The items are sterilized by the EtO gas. The exposure time provides the required EtO exposure and penetration to assure sterility by ensuring the gas has time to reach all areas of the

sterilization load. More complex sterilization loads (i.e., loads with devices with complex shapes) generally need longer exposure times.

Vacuum and Nitrogen Flushing - A vacuum is created to remove the sterilant. Nitrogen is used to “wash” the EtO from the devices to ensure the residual EtO gas concentration is below the flammable limit (approximately 3%). The diagram in the figure above has a series of partial vacuums and nitrogen washes.

Ventilation - The chamber is ventilated. All sterilization gas is removed from the chamber.

Aeration - Heated aeration is often used to accelerate out gassing of exposed sterilization loads and to contain and eliminate residual EtO emissions. This process step can help ensure that EtO sterilized medical devices meet the standard acceptable limits for EtO residuals as specified in ANSI/AAMI/ISO Standard 10993-7 - *Biological evaluation of medical devices -- Part 7: Ethylene oxide sterilization residuals*.⁵

EtO processes require relative humidity in the 30-80% range for optimum sterilization effectiveness. The rate of the EtO microbial kill process depends on the process parameters including time, temperature, humidity, and EtO concentration.

The EtO sterilization process parameters required to achieve sterilization of a device are determined by the challenges presented by the load to be sterilized and the physics and engineering of the EtO sterilizer. The material make-up of the device, the native microorganism bioburden on the device, physical features of the device (e.g., matted surface, hinges, lumen dimensions if applicable, occluded regions), the packaging materials and configuration, and the physical configuration of the load within the sterilizer chamber all impact the accessibility of the EtO to internal areas of the device, the EtO concentration within the load, and the required conditions to achieve sterilization of the device. The sterilizer chamber volume, the process temperature, the partial pressure of EtO, the EtO concentration, and the partial pressure of water vapor within the sterilizer impact the delivery of EtO to the device and the sterilization conditions.

The design of the load intended to be sterilized in the chamber plays a significant role in determining the sterilization conditions, including the amount of EtO to be used. The sterile barrier system containing the devices and any accessories, printed material such as the instructions for use, other items in the packaging system, and the configuration of the packaged devices within the sterilizer chamber will impact the conditions required to achieve sterilization of the device. For example, paper materials readily absorb EtO gas and a sterilization load may contain a large amount of paper packaging and printed instructions for use.

After the exposure phase of the sterilization process is completed, the EtO gas may continue to be absorbed into the load while the majority of the EtO gas is evacuated from the sterilization chamber through a gas purge and air is introduced into the sterilization chamber followed by an inert gas (i.e. nitrogen) backwash. The aeration and residuals mitigation steps reduce the amount of EtO and its toxic degradation products, ethylene chlorohydrin and ethylene glycol, on device materials and evacuate them from the chamber. Ethylene chlorohydrin and ethylene glycol are residual products that form during and after EtO sterilization; they result from the decomposition of EtO in the chamber and on the sterilization load over time. Typically, this step is performed at an elevated temperature to aid in the removal of these residual chemicals from the load and the chamber.

As mentioned in earlier sections of this summary, one of the most important reasons for using EtO is its material compatibility. Of all sterilization modalities, EtO is compatible with the widest range of materials, such as plastics, adhesives, metals, glass, botanicals, that are commonly used in medical devices. The following Table, “General compatibility of various types of materials with EtO”, which is taken from the Association for the Advancement of Medical Instrumentation (AAMI) Technical Information Report 17 (TIR17) – *Compatibility of materials subject to sterilization*, highlights the broad range of materials compatible with EtO.⁶

Table 2: General compatibility of various materials with EtO. Excerpted from *AAMI TIR17 – Compatibility of materials subject to sterilization* (reproduced with permission)

Material type	General compatibility
Thermoplastics	Most thermoplastics are EO sterilized with limited effects.
Thermosets	Most thermosets are EO sterilized with limited effects.
Elastomers	Most elastomers are EO sterilized with limited effect(s).
Adhesives	Most adhesives are EO sterilized with limited effects.
Metals	Most metals are EO sterilized without any corrosion or dulling of sharp metal instruments.
Glass and Ceramics	Most glass and ceramics are sterilized without any erosion.
Silicone	Most silicones are sterilized with limited effects (but EO residuals in implantable prostheses might be unacceptable).
Liquids	Liquids are not typically sterilized with EO.
Contact surfaces	The effects on contact surfaces of anti-blocking EO sterilization will depend on the type of contact surface (e.g., smooth vs. rough), type of material, and the nature of the anti-blocking agent.
Cellulosics	Most cellulosics are EO sterilized with minimal effects.
Bioabsorbables	Most biosorbables (e.g., poly-L-lactide [PLLA], polylactic acid [PLA], polyhydroxybutyrate [PHB], polyglycolic acid [PGA], polylactic-co-glycolic acid [PLGA], and polycarbonate [PCL]) can be sterilized with EO, depending on its concentration, humidity, and temperature.

In addition to its chemical compatibility with these materials, EtO cycles are run at low temperatures, making this sterilization modality compatible with devices that are heat-sensitive; for example, some polymeric device materials may not be suitable for sterilization at higher temperatures (e.g., reusable flexible endoscopes). As a gaseous sterilant, EtO is suitable for devices that are moisture-sensitive. Its reactivity with some materials limits its use for sterilization of liquids, pharmaceuticals, and biologics, although EtO is often used to surface-sterilize the containers or delivery systems these products are packaged in. Also, some materials retain EtO residuals longer than others, requiring longer aeration times. These EtO-retaining materials may present a biocompatibility concern based on residual testing per ANSI/AAMI/ISO 10993-7 – *Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals*.⁵ In addition, the use life of a reusable device may be limited as many materials, such as adhesive compounds, can degrade following multiple EtO sterilization cycles.

As previously described, FDA does not directly regulate industrial sterilizers. However, FDA reviews the validation and output of industrial sterilization processes as part of the premarket review process. For example, industrial sterilization process validation information for a 510(k)-cleared device is reviewed to ensure that the process has been validated with an acceptable method to support an assurance of device sterility.⁷ However, the installation, maintenance, and industrial emissions for an industrial sterilizer are not reviewed by FDA as these aspects of industrial sterilization are not within the regulatory purview of FDA per the Agency’s regulatory authority.

Potential methods for reducing emissions from EtO sterilization processes

Potential options for reducing EtO emissions during medical device sterilization processes will be discussed during the panel meeting. In general, stakeholder groups have explored options which involve:

- reducing EtO emissions while continuing to use altered EtO sterilization processes and industrial infrastructure;
- increasing utilization of existing, non-EtO industrial sterilization infrastructure (e.g. gamma radiation, electron beam radiation, etc.); and
- utilizing other sterilization modalities that do not currently have extensive industrial capacity.

Below is a brief overview of potential options for reducing EtO emissions while continuing to use existing EtO sterilization processes and industrial infrastructure. More detailed information will be provided by invited speakers during the Advisory Committee Panel Meeting.

- It may be possible to reduce the amount of EtO emitted by industrial sterilization of medical devices by manipulating critical process parameters, such as sterilization time, reducing EtO concentration, and increasing temperature. Making existing processes more efficient by changing cycle parameters may allow for reduced EtO use. However, some medical devices, such as those made from temperature sensitive plastics, may not be compatible with higher temperatures.
- The design of the sterilization load (the medical devices being sterilized) may be changed to decrease the amount of EtO needed to sterilize the load. For example, the packaged devices may be arranged in the sterilization chamber to increase the exposed surface area, making sterilization more efficient. Also, paper-based materials are ready absorbers of EtO gas. Reducing the amount of paper materials in the sterilization load, such as paper packaging and instructions, may support reduced EtO use.
- EtO sterilization processes are “validated” -- that is, it is demonstrated that the sterilization process is reducing bacterial load to a target level. One of the most common methods used to validate an EtO sterilization process, the half-cycle/overkill method, relies on the complete sterilization of 10^6 resistant microorganisms in half the time of the full EtO sterilization cycle.⁸ This validation method supports an assurance of sterility, but may result in the use of more EtO gas than is technically needed to sterilize the load because the natural device bioburden may be less of a challenge than 10^6 resistant microorganisms. Additionally, some devices are sterilized using validated cycles that are designed to sterilize more challenging devices; this practice may result in using more EtO than needed. Sterilization process validation methods could be developed that are more supportive of reduced EtO use compared to commonly used methods. For example, ANSI/AAMI/ISO Standard 11135 - *Sterilization of health care products — Ethylene oxide* describes a validation method that combines the known resistance of 10^6 resistant microorganisms in a biological indicator with knowledge of the microorganism bioburden on the device (numbers and resistance of organisms). This information can be used to establish the sterilization process parameters for that specific device and may support reduced EtO use compared to the half-cycle/overkill validation method.

- Currently, many EtO sterilization processes utilize gas scrubbing or EtO abatement methods to reduce the EtO concentration in the process air output before the air is released to the environment. However, these mitigation steps are not universal for all EtO sterilization processes. Strategies such as redirecting gas flow through scrubbers or EtO abatement technologies may be effective methods for reducing EtO that is released into the environment in the air output of the sterilization processes by increasing process controls. Similarly, additional abatement steps during sterilization load aeration or sterilized medical device transport may help reduce EtO emissions to the environment.

V. Industrial Sterilization of Medical Devices: Other Modalities

Sterilization of Medical Devices with Radiation

Gamma irradiation:

Gamma irradiation is a commonly used industrial sterilization process for medical devices. It is considered favorable for use in industrial processes due to its short processing time, ability to penetrate multiple layers and types of packaging, and its compatibility with a variety of materials (though fewer than EtO).

Gamma radiation is emitted from an atom or a molecule when its energy level drops. Sterile processing using gamma irradiation is based on self-disintegration of Cobalt-60. Cobalt-60 is stored and used under strict standards and is regulated by the Nuclear Regulatory Commission. Gamma irradiation kills bacteria by destroying DNA, preventing bacterial division. Additionally, the effectiveness of gamma irradiation is not influenced by humidity, temperature, or pressure and it does not significantly heat the loads being sterilized. Gamma sterilization processes do not have sufficient energy to cause sterilized loads to become radioactive.

Gamma sterilization is based on the dose of radiation absorbed and is generally measured in kilogray (kGy) units. Typical doses used for sterilization are 25 kGy; in comparison, those used for cancer radiotherapy range from 20-80 Gy. The radiation dose at various locations in the load depends on the thickness of the load. Loads intended for sterilization are configured to ensure that the dose of radiation falls within an acceptable range to ensure minimum exposure sites on the load are consistent with the expected sterility assurance level and the load will not be damaged by the radiation dose on the maximally exposed sites.

Gamma irradiation sterilization processes are validated by characterizing the load and establishing the bioburden on the products intended for sterilization within the load. The maximum allowable dose of radiation that the device and/or packaging can tolerate without damage would be determined.

The sterilization dose is established from either knowledge of the resistance of the bioburden to the dose or substantiation of a predetermined sterilization dose. The sterilization validation process may include:

1. Tests of sterility using product challenged with increasing doses of radiation to characterize bioburden resistance to the sterilization process

2. Tests to determine the sterilization dose needed to support the intended sterility assurance level and/or sterility testing using a verification dose (radiation dose that provides a fraction of the lethality of the intended sterilization dose)

X-ray sterilization:

X-ray sterilization is another radiation-based sterilization method. X-rays are high-energy electromagnetic radiation released when accelerated electrons are slowed by interacting with targeted elements such as tungsten. In sterilization processes, x-rays are generated by machines and provide radiation in a specific uniform direction to the sterilization load. X-ray sterilization has similar penetration capability to gamma processes, but currently is not widely utilized. X-ray sterilization processes are validated with similar methods to gamma irradiation processes and include characterization of the load, determination of the natural product bioburden, evaluation of device compatibility with the sterilization process, and determination of the sterilization dose.

Electron beam sterilization:

Electron beam (E-beam) sterilization, along with gamma irradiation and X-ray sterilization, is a radiation-based sterilization method. Electron beams are streams of accelerated electrons created using magnetic fields. Electrons have mass (versus X-rays and gamma rays) and have limited penetrating capability compared to other radiation sterilization modalities. The radiation dose in E-beam sterilization processes is a function of the design and engineering of the sterilizer, the energetics and dimensions of the E-beam, the load characteristics (density and thickness), and the speed of the conveyor. E-beam sterilization processes are validated with similar methods to gamma irradiation and X-ray sterilization processes and include, characterization of the load, determination of the natural product bioburden, evaluation of compatibility with the sterilization process, and determination of the sterilization dose. However, the penetration differences between E-beam and gamma/X-ray sterilization processes require very different load configurations for effective sterilization.

Sterilization of Medical Devices with Steam

Steam sterilization is based on microbial inactivation kinetics wherein a highly resistant organism, such as *Geobacillus stearothermophilus* spores, is used as a biological indicator (BI) to determine a Sterility Assurance Level (SAL). An SAL of 10^{-6} must be demonstrated; that is, the probability that a single spore that has been subjected to sterilization nevertheless remains nonsterile is one in a million. The BIs are designed with a defined challenge to the sterilization process and represents the greatest challenge to the load.

Steam sterilization has limited industrial applications but is an effective method for sterilization of certain device types. Steam sterilization processes allow effective penetration of the steam sterilant and heat to all parts of a medical device. The market share for industrial steam sterilization as it relates to medical products is <5%. Steam sterilization is used for sterilizing heat stable liquids. Polymer materials such as polypropylene, polycarbonates, polyurethanes, Tyvek, and other materials are heat stable and can be sterilized using steam sterilization method. However, industrial steam sterilization represents only a small percentage of the industry because many materials used in medical devices requiring sterilization are heat sensitive and not compatible with the high temperatures of the steam sterilization process. High temperatures (typically 121-134°C) can damage some polymers, corrode metals, or cause combustion of lubricants in the devices. As a mitigation for this, some polymer-based materials may be made compatible

with the steam sterilization process if the selected temperature for the steam sterilization is matched with the polymers' heat sensitivity. In addition, the corrosion of metals can be mitigated in some cases by applying non-corrosive solutions on metal surfaces before subjecting them to steam sterilization.

The types of steam sterilizers used to sterilize medical devices include gravity displacement sterilizers and pre-vacuum sterilizers. In gravity displacement sterilizers, steam is pumped in the sterilization chamber at the top or sides of the chamber which forces out the air from the bottom of the chamber through a vent. Gravity steam sterilizers use lower temperatures compared to pre-vacuum sterilizers and are not as efficient in penetrating into porous items due to their inefficient removal of air from the loads. In pre-vacuum sterilizers, the air from the sterilization chambers is removed by vacuum pump enabling the steam to penetrate porous loads efficiently.

Steam sterilization is dependent on four critical parameters such as quality of steam (the proportion of steam vapor vs condensate), exposure temperature, exposure time, and pressure to achieve microbial kill. Within the sterilization chamber specific temperatures must be achieved to ensure microbial kill and the steam sterilization cycle can be monitored through biological, chemical, and mechanical means. Some example steam sterilization cycles used to sterilize medical devices are 121°C (250°F) for 30 minutes in a gravity displacement cycle, 132°C (270°F) for 4 minutes or 135°C (275°F) for 3 minutes in a pre-vacuum cycle. Depending on the medical device loads (metal, lumens, plastic, complexity of the device, weight, etc.) firms may use other exposure temperatures and parameters for terminal sterilization of single use devices. To establish specific steam sterilization cycle settings, critical parameters are considered based on the type of materials in the medical devices and their loads.

Summary Overview of Common Industrial Sterilization Modalities

Table 3: Summary information for common industrial sterilization modalities

	Ethylene Oxide (EtO)	Radiation	Steam
Approximate percentage of sterile medical devices sterilized with the modality	~50%	~45%	<5%
Sterilant source	EtO gas	gamma radiation (cobalt-60), x-ray radiation, electron beam radiation	pressurized steam
Critical process parameters	gas concentration, temperature, humidity, exposure time	radiation dose	steam quality, pressure, temperature, exposure time
Generalized examples of medical devices sterilized with this modality	single use devices, reusable devices, surgical kits, electronic devices, heat-sensitive devices, devices with hard-to-reach crevices	some single use devices, heat-sensitive devices, radiation-resistant plastic devices	heat/moisture-resistant devices, some metal devices

VI. Sterilization Modalities with Unknown Industrial Infrastructure

Although some of these modalities have been utilized as a terminal sterilization process for a small number of devices, the total availability, existing infrastructure, and the scalability of these modalities is not well known with respect to industrial sterilization of medical devices. The ability of these modalities to serve as an alternative to industrial EtO sterilization is not clear and a discussion of the feasibility of leveraging these modalities is an objective of this Medical Devices Advisory Committee meeting.

Hydrogen Peroxide

Hydrogen peroxide sterilization is a low temperature sterilization process that utilizes hydrogen peroxide vapor. The vapor fills the sterilization chamber, penetrates the device and sterilizes exposed surfaces. Hydrogen peroxide sterilization is one of the few commonly used low-temperature sterilization modalities, making it an option for sterilization of heat sensitive devices. Hydrogen peroxide sterilization has cycle times typically running less than an hour. Hydrogen peroxide is compatible with a wide range of materials commonly used for medical devices. Hydrogen peroxide sterilizers must adhere to OSHA's Permissible Exposure Limit (PEL), which is 1 ppm over an 8-hour period. Since these systems are self-contained, exposure to workers is limited. The only byproducts of the process are water and oxygen.

Hydrogen peroxide sterilization is available as either vaporized hydrogen peroxide (VHP) on its own or vaporized hydrogen peroxide excited into plasma. In some systems, vaporized hydrogen peroxide is combined with ozone. The sterilizers run under vacuum to increase exposure and consist of three phases – conditioning, sterilization, and aeration. The conditioning phase is intended to ensure the load is dry and all air is removed, which is critical for this modality to prevent sterilant condensation or absorption. Vaporized hydrogen peroxide is then introduced in a series of pulses. This phase includes applying a vacuum, injecting the vaporized hydrogen peroxide, diffusion of the VHP throughout the chamber killing surface microorganisms, and venting to equalize the pressure. This process is the same for both VHP-only, VHP and ozone, and VHP-plasma sterilizers. For sterilizers that utilize plasma, VHP is pulsed and, following diffusion, is broken apart by the generation of an electromagnetic field, generating a low-temperature plasma cloud of free radicals that reacts with molecules essential for normal metabolism of microorganisms. VHP cycles use a “block” structure since each pulse introduces the same amount of hydrogen peroxide which is then removed, with the cycle being lengthened or shorted by the addition/removal of these pulses. Aeration then ensures all residual hydrogen peroxide is removed.

VHP sterilization modalities have limitations, including limited chamber sizes with chambers that are smaller than most autoclaves. The small chamber sizes currently prohibit scaling up to sterilize large loads at an industrial level. In addition, hydrogen peroxide has material compatibility limitations. For example, as a strong oxidant, hydrogen peroxide is reactive with copper and cellulose. This is a challenge as both materials are utilized in medical devices. Many packaging and labeling materials utilize cellulose, which readily absorbs hydrogen peroxide, limiting the utility of this modality for devices with cellulose-based packaging and labeling. Nylons and plastics may become brittle following multiple exposure to a VHP cycle. Micro-condensation of the sterilant can also occur and while this condensate still has microbiocidal activity, it is not controlled and can impact sterilization efficacy. These systems are also sensitive to small changes in process parameters. Critical parameters for hydrogen peroxide sterilization are gas concentration, temperature, time, and pressure. For plasma systems, monitoring of the applied radiofrequency (RF) energy

is also needed to ensure adequate generation of plasma. Changes to any of these parameters may greatly impact sterilization efficacy.

There currently are no recognized consensus standards for this modality. Currently, manufacturers of VHP-based sterilizers are directed to ANSI/AAMI ST58 – “Chemical sterilization and high-level disinfection in health care facilities”. There are similarly no recognized standards for the development of biological indicators for this modality.

Nitrogen Dioxide

Nitrogen Dioxide (NO₂) sterilization is a chemical-based sterilization method. The active sterilant is the gas phase of NO₂, which exists above 21.2°C. The gas phase of NO₂ can readily penetrate device packaging and sterilize medical devices by creating single strand breaks in DNA. This sterilization process is validated using the overkill method (similarly to EtO) to achieve a sterility assurance level of 10⁻⁶. The residues present after sterilization are nitrogen-based and are at relatively low levels because of the sterilization mechanism. NO₂ is compatible with many medical device materials except for polyurethane, nylon, polyacetal, copper (and alloys), nitinol, and cellulose-based materials.

Chlorine Dioxide

Chlorine Dioxide (ClO₂) sterilization is a chemical-based sterilization method. The active sterilant is the gas phase of ClO₂. The gas phase of ClO₂ can readily penetrate device packaging and sterilize medical devices through an oxidative mechanism at low sterilant concentration at room temperature and at atmospheric pressure. This sterilization process is validated using the overkill method to achieve a sterility assurance level of 10⁻⁶. The residues formed during this sterilization process are chlorine dioxide, chlorates, and chlorite that have low toxicity concerns from the reported literature. Although material compatibility information is limited, ClO₂ is not known to be incompatible with the most commonly used materials in medical devices such as stainless steel and some polymers.

Vaporized Peracetic Acid

Vaporized Peracetic Acid (CH₃CO₃H) sterilization is a chemical-based sterilization method. The active sterilant is the reactive molecules found in the vapor phase between acetic acid and peracetic acid. The reactive molecules found in the vapor phase readily penetrate device packaging and sterilize medical devices through an oxidative mechanism that denatures proteins, disrupts cell wall permeability, and oxidizes sulfhydryl and disulfide bonds in proteins, enzymes, and other metabolites at low temperatures. This sterilization process is validated using the overkill method to achieve a sterility assurance level of 10⁻⁶. The residues formed during this sterilization process are acetic acid, peracetic acid, water, and oxygen, which have low toxicity concerns. CH₃CO₃H is known to be compatible with a wide range of materials used in the construction of medical devices such as stainless steel and many polymers.

VII. FDA Questions

The questions we propose fall under three broad categories that discuss: Impact on the Medical Device Ecosystem, Optimization of EtO, and Potential Alternatives to EtO.

Impact to greater medical device ecosystem

1. If EtO sterilization is reduced, eliminated or replaced to a different sterilization modality, how can the impact to healthcare delivery organizations be minimized?
2. What can FDA do to help mitigate and prevent device shortages due to reduced device sterilization capabilities?

Optimization of EtO (reducing use and emissions)

3. How can changing EtO sterilization cycles or sterilization loads reduce EtO use while maintaining effective sterilization? Can the panel provide a recommendation for which methods appear to be the most promising?
4. Can new or different methods of validating EtO sterilization cycles potentially result in a reduction of EtO use while still maintaining an effective sterilization process? If so, how?
5. Should sterilization of some medical devices to a less rigorous sterility assurance level (e.g. 10^{-5} , 10^{-4} , etc. instead of 10^{-6}) be considered as part of the approach to reduce sterilant use? How do you see this changing the patient risk profile for sterile devices if a different sterility assurance level is determined to be acceptable?

Potential alternatives to EtO

6. Are there existing large-scale industrial sterilization modalities that can take over a portion of the EtO sterilization performed for medical devices in the short or long term? If so can the panel provide a discussion of the path forward for these modalities? If not, what are the barriers and challenges preventing wider utilization of these modalities?
7. Are there alternative sterilization methods being developed that can take the place of EtO sterilization processes with respect to scalability and material compatibility? If so can the panel provide a discussion of the path forward for these modalities? If not, what are the barriers and challenges preventing large-scale industrial utilization of these modalities?
8. How can FDA help implement adoption of these EtO reduction or EtO replacement strategies and facilitate reduction of EtO emissions within our regulatory framework?
9. Can the panel identify devices or device types that would be difficult to sterilize without using EtO that may be amenable to the application of alternative sterilization modalities?

10. Does the panel have any other recommendations for reducing EtO risk without causing medical device shortages?

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