## Industrial Sterilization of 20 Billion Single-Use Medical Devices by ETO: Consequences of ETO Closures and Alternative Technologies

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#### DISCLOSURES 2022

- Consultations
  - PDI (Professional Disposables International), Sterigenics
- Honoraria
  - PDI
- Other
  - Kinnos, Ideate Medical

More than 20 billion devices sold in the US every year are sterilized with ethylene oxide, accounting for approximately 50% of the devices that require sterilization. Concerns about ETO emissions have resulted in certain state actions against sterilization facilities (i.e., ETO closure) that may impact use of ETO to sterilize medical devices. NE Sharpless, FDA, October 2019

How to resolve the need for sterile medical devices in health care and efforts to ban ETO due to controversial effects on neighboring communities?



- Review history of sterilization and sterile medical devices
- Review why we need safe and effective sterilization
- Consider the consequences to health if ETO not widely available
- Discuss the adv/disadv of ETO, radiation and other technologies
- Conclusions



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**Empirical Observations** 



- Hospitals were notoriously unclean
- Entering the OR in 1865 was a "life-or-death" gamble
- Gangrene, septicemia, and post-operative infection affected almost half of those operated on.
- Doctors arrived in street cloths and without even washing hands
- The problem was so pressing that there was talk of abolishing surgery altogether in hospitals









#### Late 19<sup>th</sup> century pioneers

- Louis Pasteur-1857, fermentation caused by microorganisms
- Louis Pasteur-1862, heat inactivation/pasteurization
- C. Chamberland-1879, autoclave
- R. Koch-1880s, Koch postulates
- E. Bergmann-1870s, heat sterilization of surgical instruments



Joseph Lister

Empirical Observations

- Joseph Lister, a surgeon, discovered the work of Louis Pasteur, a French chemist
- When he read fermentation was due to germs, microbes invisible to the eye, he sensed the same could explain the infection of wounds.
- Lister looked for a chemical substance to annihilate the germs and promoted the idea of sterile surgery.
- Lister successfully introduced carbolic acid (now known as phenol) to sterilize surgical instruments and to clean wounds.
- Listerine mouth wash is named after him for his work in antisepsis.

#### Historical Perspective of Sterilization Empirical Observations

Lister implemented three practices

- Washed his hands with carbolic acid and wore gloves
- Swabbed the solution on wounds
- Sprayed surgical instruments with carbolic acid
- Reduction in mortality
  - From 1864-1866, Lister lost 46% of his surgical patients
  - From 1867-1870, he lost "only" 15%
  - By 1877, he dropped the death rate to 5%

Joseph Lister

#### World War II



#### Following World War II

- Confluence of scientific and technological advancements in microbiology, medical products, polymer chemistry, radiation physics, and food preservation technologies
- Led to low-temperature sterilization technologies, radiation and ethylene oxide
- Today, 60 years later, most commonly used modalities of terminal sterilization processing of medical products are radiation and ethylene oxide



- By 1940, ETO was being used in hospitals
- Dr. Charles Rush, US Army, spearheaded the application of ETO gas
- Devices increasingly made of plastics
- Recognized as major advancement
- From 1950s to 1990s the method of sterilization for heat-sensitive devices

Devices delivered in a sterile state must have been manufactured and sterilized by an appropriate, validated method

### **Regulation of Medical Devices by FDA**

- Medical devices are regulated by the FDA
- Intended to provide consumers with safe and effective medical device
- FDA "Sterile Device Guidance" requires certain information be submitted to the FDA for 510(k) clearance if labeled as sterile
- The sterility assurance level (SAL) refers to the probability that an a device will be non-sterile (SAL 10<sup>-6</sup>, no more than a 1 in 1 million chance that the sterilized product is in a non-sterile condition [12 log<sub>10</sub> reduction)



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### Why Do We Need Safe and Effective Sterilization?

- Prevent HAIs, it is essential that medical devices are sterilized before use
- Critical items-contact with sterile tissue or sterile body fluid flows through them, must be sterile
- ~40 billion medical devices sterilized per year
- Industrial sterilization
  - ETO~50% (20 billion medical devices per year)
  - Radiation
    - ♦ Gamma radiation~40%
    - Electron-beam~4.5%



## Concerns with Medical Device Availability Due to Sterilization Facility Closures

NE Sharpless, FDA, October 2019

- FDA became aware that the Illinois EPA issued an order for an Illinois ETO industrial sterilization facility to close due to allegations about the levels of ETO in the air around the facility (February 2019)
- The facility provided ETO sterilization services to over 100 medical device manufacturers and sterilized more than 500 types of medical devices
- FDA recognized the effect on any elimination or severe restriction of ETO would potentially threaten the entire health care system as shortages could result putting patients at infection risk or inadequate care.

### FDA's Role in Assessing Medical Device Sterility

FDA Sterile Device Guidance, January 2016; FDA Executive Summary, November 2019

- Medical devices classified based on risk the device poses to the patient
  - Class I, lowest risk, subject to general controls like labeling, adverse event reporting
  - Class II, intermediate risk, most are reviewed by FDA prior to market under 510k, PMA
  - Class III, highest risk, require Premarket Approval (PMA)
- Ensuring device sterilization is an important part of the FDA's assessment of a device's safety profile

### FDA's Role in Assessing Medical Device Sterility

FDA Sterile Device Guidance, January 2016; FDA Executive Summary, November 2019

- FDA Sterility Guidance provides examples of some of sterility information assess as part of a 510(k) review:
  - A description of the sterilization method
  - The amount of residual sterilant on the device
  - A description of the sterilization validation method
  - A description of the sterile barrier system (packaging)
- FDA ensures medical devices are sterilized using a validated, effective and repeatable process
- EPA controls emissions and protects public from significant risk of ETO exposure

### Most Common Methods for Terminal Industrial Sterilization Processing of Medical Devices

- ETO~50% (20 Billion)
- Radiation
  - Gamma~40%
  - Electron beam~4.5%
  - X-ray<5%

- Other sterilization technologies
  - Steam
  - Hydrogen peroxide
  - Vaporized peracetic acid
  - Chlorine dioxide
  - Nitrogen dioxide
  - Supercritical carbon dioxide

### Why is ETO Uniquely Effective?

FDA Panel, 2019

- Broad material and device compatibility
- Penetration through multiple layers of packaging (barrier to microbes)
- Process flexibility (adjustable parameters)
- Large quantity of devices and mixed loads can be sterilized at once
- Long history of use and regulatory familiarity
- Effective bactericidal, virucidal, mycobactericidal, fungicidal, sporicidal
- Permeates dense loads
- Long history of success, product penetration, safe for the consumer as residuals below acceptable thresholds

### Penetration through multiple layers of packaging Permeates dense load; Large quantity of devices





#### **Medical Devices Sold As Sterile**

Procedure Kit (all components must be compatible)





**Single Use Sterile Surgical Instrument** 

#### FDA Response to Potential Medical Device Shortages

(FDA taking steps to ensure access to medical devices that are safely and effectively sterilized)

- First, FDA Innovation Challenges (August 2019)
  - Challenge 1-Identify sterilization alternatives (long-term)
  - Challenge 2-Reduce ETO emissions (short-term)
  - FDA will work with 12 applicants
- Second, FDA Panel (November 2019) of experts to address challenges associated with ETO emissions and discuss sterilization of medical devices, shortages, and alternative technologies
  - Panel had specialties in biomaterials, biomechanics, biomedical engineering, human factors, infection preventionist, gastroenterologists, chemical engineers, infectious diseases, anesthesiologists, endocrinologists, validation and sterile processing, as well as patient advocates, industry representatives, and regulatory affairs consultants.

### FDA Panel-ETO, November 6-7, 2019

https://www.fda.gov

- ETO is the only effective method for sterilization of certain medical devices due to their material compatibility (e.g., polymer, plastics), size, shape, and complexity.
- ETO penetrates difficult-to-reach places of medical devices (e.g., lumens of catheters), and packaging to allow sterilization.
- Uniquely effective: long-history of success; permeates dense loads; large quantity of devices at once; process flexibility
- For these reasons (in addition to its effectiveness and dependability for over 70 years), ETO has been successfully used for sterilization of reusable and single-use medical devices.



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### **Shortages from Lost ETO Sterilizing Capacity**

FDA Executive Summary, November 2019

- Patients will lose access to important devices if ETO is not available
   50,000 devices can be sterilized by ETO only (per GUDID)
  - ~50% of all manufactured medical products sterilized by ETO
  - 96% of all surgery kits (75-100 components)- ETO is the only method compatible with all of the products (e.g., lumens, cellulose-based, cotton, plastic, Teflon)
  - Capacity in industrial ETO facilities is >90%. If 2 facilities close, capacity exceeded.
  - To sterilize a device at another ETO facility, not simply a matter of identifying a site as medical device needs to be re-validated each one at the new site (months/years)

### **Shortages from Lost ETO Sterilizing Capacity**

FDA Executive Summary, November 2019

- If 50% of all medical devices would not longer be available to patients and users, the risk (morbidity/mortality) would be catastrophic
- If common medical devices used to prevent SSIs, UTIs, CLABSI, VAPs (e.g., catheters, instruments, tubing, syringes, etc.) were non-sterile and contaminated with viable bacteria, the infection risk would increase dramatically.
- Disinfection lacks the robustness and safety achieved by sterilization procedures. If the severity of shortage of industrial ETO sterilized medical devices required treatment by suboptimal methods, the infection rate would drastically and quickly increase. The infections would require antibiotic therapies, which would increase antibiotic resistance.



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- Other sterilization technologies
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  - Chlorine dioxide
  - Nitrogen dioxide
  - Supercritical carbon dioxide

### **Steam Sterilization**

#### Advantages

- Nontoxic to patient, staff, environment
- Cycle easy to control and monitor
- Rapidly microbicidal
- Least affected by organic/inorganic soils
   among sterilization processes listed
- Rapid cycle time
- Penetrates medical packing, device lumens
- Long history of safe and effective

- Deleterious for heat-sensitive instruments/devices
- Microsurgical instruments damaged by repeated exposure
- May leave instruments wet,
- causing them to rust
- Potential for burns
- Not compatible with most medical devices because plastics heat sensitive

### **Ethylene Oxide**

#### Advantages

- Penetrates packaging materials, device lumens.
- Best materials compatibility
- Products can be processed in sealed, final packaging
- ~50,000 medical devices validated
- Simple to operate and monitor
- Can sterilize products with batteries and electronics
- Long history of safe and effective use
- Broad microbicidal activity

- Requires aeration time to remove ETO residue
- ETO is toxic, a carcinogen, and flammable
- ETO emission regulated by states (9)/countries. Catalytic converters and acid water scrubbers reduce ETO emissions.
- ETO 1ppm TWA employee exposure
- Lengthy cycle/aeration time

### Hydrogen Peroxide

#### Advantages

- Safe for the environment and healthcare personnel
- Leaves no toxic residuals
- Cycle time is <70 minutes and no aeration necessary
- Used for heat- and moisture-sensitive items since process temperature <50°C</li>
- Simple to operate, install (208 V outlet), and monitor
- Compatible with most medical devices
- Only requires electrical outlet
- Microbicidal efficacy data
- Able to sterilize electronic components and batteries

- Cellulose (paper), linens and liquids cannot be processed
- Very few single-use medical devices (34) have been validated
- Restrictions based on lumen internal diameter and length (see manufacturer's recommendations)
- Sensitive to small changes in process parameters
- Requires synthetic packaging (polypropylene wraps, polyolefin pouches) and special container tray
- Scalability or chamber size challenging
- Hydrogen peroxide may be toxic at levels greater than 1 ppm TWA

### Radiation (Gamma, X-Ray, Electron beam)

#### Advantages

- Compatible with many medical materials
- Products can be processed in sealed, final packaging
- Penetrates medical packaging
- Microbicidal data
- Long history of safe and effective use
- No residue on sterilized products
- No regulated emission

- Individual plastics need to be assessed
- Common plastics (Teflon, PFA, PTFE, PP) must be avoided
- Adverse effects on glues and adhesives
- Gamma requires a nuclear reactor, expensive
- Source replenishment and requalification required (Cobalt-60)
- Licensing, installation, security, waste disposal challenging
- E-beam limited penetrating power

# Material Compatibility for Materials in Use in Medical Devices Subject to ETO and Radiation (1 or 2 cycles)

Raw material designation	Radiation	ETO
Acrylobutadiene styrene (ABS)	3	4
Cellulose ester	2	4
Cellulose, paper, cardboard	2-3	4
Ethylene propylene diene monomer (EPDM), synthetic rubber-elastomer	3-4	4
Fluoropolymers (e.g., polytetrafluoroethylene-PTFE)	1	4
Perfluoroalkoxy (PFA)	1	4
Polyacetal, or acetal, or polyoxymethylene (POM)	4	4
Polyamides (PA), nylon	2-3	4
Polycarbonate	3-4	4
Polyethylene	3-4	4
Polypropylene	2-3	4
Teflon	1	4

#### AAMI Tech Inform Report 17:2017; 4-completely compatible; 1-do not use

### **Vaporized Peracetic Acid**

#### Advantages

- Used for heat sensitive items
- Compatible with most plastics
- Potential for in-house sterilization

- Poor penetration power; can penetrate primary packaging but not end package
- Not compatible with cardboard
- Limited experience, must be evaluated for compatibility, product performance, residuals, microbial efficacy, scalability
- Little or no published information
- Very few single-use medical devices (7) validated
- FDA not determined to be adequate

### Nitrogen dioxide

#### Advantages

- Used for heat sensitive items
- Compatible with most plastics
- Potential for in-house sterilization
- No cytotoxic residues

- Poor penetration power; can penetrate primary packaging but not end package
- Not compatible with cardboard
- Limited experience, must be evaluated for compatibility, product performance, residuals, microbial efficacy, scalability
- Little or no published information
- Very few single-use medical devices (7) validated
- FDA not determined to be adequate
- Surface sterilant (does not penetrate)

### **Chlorine dioxide**

#### Advantages

- Used for heat sensitive items
- Primary use for chlorine dioxide is room decontamination
- Does not damage electronics and batteries
- Rapid aeration

- Poor penetration power; can penetrate primary packaging but not end package
- Not compatible with cardboard
- Limited experience, must be evaluated for compatibility, product performance, residuals, microbial efficacy, scalability
- Little or no published information
- Very few single-use medical devices (7) validated
- FDA not determined to be adequate
- Surface sterilant (does not penetrate)

## How many medical devices are validated for ETO and other sterilization methods?

# Global Unique Device Identification Database (GUDID)

- Administered by the FDA, established in 2013
- Repository of detailed medical device information
- Designed to identify and trace medical devices sold in the US
- 64 data elements
- Over 2 million records of medical devices sold in the US
- Searchable data base of device identification information

# Devices Labeled in Single-Use, In Commerce, and Packaged as Sterile (per GUDID, April 2022)

Sterilization Method	Excludes Other Sterilization Methods
Ethylene oxide	49,998
Radiation (includes gamma, e-beam, x-ray)	12,177
Hydrogen peroxide	34
Steam	8,406
Vaporized peracetic acid	7
Nitrogen dioxide	0
Chlorine dioxide	5
Supercritical carbon dioxide	0



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### **ETO Closures and Alternate Technologies**

FDA Sterile Device Guidance, January 2016; FDA Executive Summary, November 2019

- ETO plays a critical role in patient health and safety
- To prevent HAIs, essential medical devices must be sterilized before use
- No sterilization technology is able to replace ETO in the short term (<10y)
- Approx 50,000 medical devices that are currently in the marketplace can only be sterilized with ETO
- If alternative sterilization technology available today, it would take decades (each devices ≥1 year) at a cost of \$1 million per device for these ~50,000 medical devices to go through FDA validation/clearance

### **ETO Closures and Alternate Technologies**

FDA Sterile Device Guidance, January 2016; FDA Executive Summary, November 2019

- The impediments include: material compatibility, complexity, infrastructure needed to utilize alternative sterilization methods in an industrial capacity, packaging used to contain the medical products and barriers intended to maintain sterility, and regulatory hurdles as every device would need to be re-cleared with the new method
- The ramifications of device shortages and using contaminated medical devices on public health would be catastrophic (extended hospitalization, worsening co-morbidities and death)

#### THANK YOU! www.disinfectionandsterilization.org



### **FDA Innovation Challenge**

#### Challenge 1 (long-term correction)

 FDA selected four participants and five submissions for this challenge to include: vaporized hydrogen peroxide, nitrogen dioxide, supercritical carbon dioxide, and accelerator-based radiation

#### Challenge 2 (short-term correction)

- FDA selected eight participants for this challenge and includes: enhanced ETO cycle design (five companies), reduced sterilant concentration, abatement strategy; and ETO-flexible chamber technology.
- Goal of this challenge is to develop strategies or technologies to reduce ETO emissions to as to be as close to zero as possible. The strategies may allow for: use of lower levels of ETO while assuring safe and effective sterilization; capture of ETO emissions and/or transformation to harmless byproducts; containment of fugitive emissions to prevent or minimize emissions into the sterilization facility or environment; and safe use of ETO while minimizing harm to sterilization workers and nearby communities

## Global Unique Device Identification Device (GUDID)

	FDA TOOLS AND RESOURCES 🔻	NIH) NATIONAL LIBRARY OF MEDICINE TOOLS AND RESOURCE	CES 🔻
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AND    Single Use  true	•	FDA Product Code       3.2mm Angle Slit Knife         FDA Product Code       Company Name: KRISHNA IMPORTS INC         Version or Model:       R-5572	
AND	•	Device Packaged As Sterile > <u>Stephens Instruments - 00810799030368</u>	_
AND   Commercial Distribution Status  In Commercial Distribution	00	Sterilization Prior To Use       3.0mm Angle Slit Knife         Company Name: KRISHNA IMPORTS INC       Version or Model: R-5570	