Shortage of Ethylene Oxide Sterilized Medical Devices: CDRH’s Role

Adam E. Saltman, M.D., Ph.D.
CDRH Medical Officer and OPEQ Shortages Lead
Topics

• Shortages 101: How and why shortages happen

• CDRH considerations and capabilities
  – Considerations and definitions
    • Shortage assessment
    • Medical necessity
    • Management plan
  – Capabilities and tools
    • Regulatory
    • Communication
How and Why Shortages Happen

• There is no formal regulatory definition of a device shortage

• CDRH working definition
  – A *device shortage* is the period of time for which the demand or projected demand for a medical device within the United States will exceed the supply or projected supply of that device.
When Demand Exceeds Supply
The Medical Device Market Under Duress

Ideal Conditions

Medical Devices in Shortage
How and Why Shortages Happen

**Increased Demand**
- Expansion of user population
- Expansion of indications for use
- Expanded coverage determinations
- Evolving practice patterns

**Decreased Supply**
- Market removal (recall)
- Voluntary market departure
- Supply chain interruption
  - Loss of raw materials, sterilization
- Manufacturing interruption
  - Natural or man-made disasters

Shortage is usually temporary, as manufacturers increase production and new firms enter the market.

Shortage may or may not be permanent, depending upon economic, regulatory, and other factors.
How Does CDRH Approach (Potential) Shortages?

Gather information
Organize, filter, analyze
Monitor, modify
Mitigate

Shortage!!
Gather Information: Evaluate the Signal

Device Landscape

- Patients
- Professionals
- User Facilities
- Registration & Listing database
- Geographic Information Systems
- Commercial space
- Group purchasing organizations
- Regulatory space
- Agencies
- Distributors
- Manufacturers
Organize, Filter, Analyze

• Tools
  – Shortage assessment
  – Medical necessity determination
  – Shortage management plan
Shortage Assessment Tool

• A formal evaluation of the likelihood that a medical device cannot be obtained in sufficient amounts should there be a market removal, withdrawal, or cessation in distribution.

• Mainly economic and logistical, not clinical
Medical Necessity Determination Tool

• Any medical device used to diagnose, treat, or prevent a serious disease or medical condition for which there is no other adequately available device or treatment that CDRH clinical staff judge to be an appropriate substitute. Off-label uses and investigational devices can be considered essential. Patient inconvenience alone is an insufficient reason to classify a device product as essential.
The Medical Necessity of a Medical Device

• Are the devices within the product code used to diagnose, treat or prevent a **serious disease or medical condition**?

• If these devices do not have a diagnosis or treatment indication, is/are it/they used as a **tool** (e.g., core medical equipment) for **life sustaining conditions or patient care**?

• Are there **alternatives available** to diagnose, treat or prevent a serious disease or medical condition?

• Are these devices made by **one or a few manufacturers**?

*Not a linear process
*Not mutually exclusive*
The Shortage Management Plan

- **Background**
  - Situational details
  - Previous experience

- **Action details**
  - Why the device is essential
  - Why access is being denied/allowed
    - Qualifications and conditions for continuing access/denial
  - Roles and responsibilities
    - FDA, manufacturer, other stakeholders
  - Mitigation plan
  - Monitoring and termination plan
    - Time, frequency, contact, other sources of information needed
  - Conditions for terminating the shortage state
Potential FDA Shortage Mitigation Actions

**Regulatory tools**
- Expedited reviews
  - Change requests for manufacturing sites, suppliers, etc.
  - Marketing applications for new, substitute products
- Discretion
  - Importation of unapproved/uncleared devices
  - Extension of expiration dates

**Communication**
- Direction and updates
  - Webpages
  - Public notifications
- Information exchange and messaging collaboration, involving
  - State and federal governmental agencies
  - Manufacturer/trade associations
  - Health professional associations
Thank You!

Adam E. Saltman, M.D., Ph.D.
CDRH Medical Officer and OPEQ Shortages Lead
Shortage of Industrial Ethylene Oxide Sterilized Medical Devices: Clinical Impact

Karoll J. Cortez, MD., MHS., FACP

Office of Surgical and Infection Control Devices
Center for Devices and Radiological Health
Shortage of Industrial Ethylene Oxide Sterilized Medical Devices: Clinical Impact

Sterilization Modality for Devices Provided Sterile to the End User

- EtO Only: 56%
- Non-EtO: 42%
- EtO + other: 2%

**Life Saving / Sustaining Devices Examples:**
- Drug eluting stents
- Catheters
- Shunts
- Deep brain stimulator – components and accessories
- Intravascular infusion ports
- Pacemakers
- Renal hemodialysis sets
- Anesthesia masks and circuits
- Left ventricular assist devices

**Daily Use Devices Examples:**
- Surgical kits
- Syringes
- Tubing sets/bloodlines
- Respirators
- Sutures
Shortage of Industrial Ethylene Oxide Sterilized Medical Devices: Clinical Impact

Flexible materials resist kinking and crushing ensuring safe ventilation and preventing damage to endotracheal tissue
Shortage of Industrial Ethylene Oxide Sterilized Medical Devices: Clinical Impact

Affected population

Tracheostomy tube in situ

Peristomal granulation tissue in a 5-y-old child with chronic tracheostomy dependence.

Karen F Watters Respir Care 2017;62:799-825
Shortage of Industrial Ethylene Oxide Sterilized Medical Devices: Clinical Impact

**FDA:**
- Works with firm. Real-time review to expedite move sterilization to new EtO facility
- Public communication with frequent updates

**Manufacturer:**
- Works with FDA: generates data at new EtO facility for real-time review
- Communicates with FDA of status and plans

**Hospital-Provider:**
- Shortage management Working groups
- Safety of patient at risk
- Planning to be prepared: Inventory, triaging,
  **Concerns:** Delays in diagnosis and treatment->increase in morbimortality.
Shortage of Industrial Ethylene Oxide Sterilized Medical Devices: Clinical Impact

- Medical devices shortages can impact patient care.
- The severity varies depending on:
  - Device type and intended use.
  - Population impacted
  - Device misallocation and hoarding
  - Effectiveness of mitigation measures
- Prompt action can reduce or prevent adverse consequences
- However, if essential, and irreplaceable devices are unavailable, physicians can’t make a diagnosis or provide life-saving therapeutic interventions.
Thank You!

Karoll J. Cortez, M.D., M.H.S.
CDRH Medical Officer
Overview of Industrial Ethylene Oxide Sterilization

Steve Elliott MSc., Scientific Reviewer, Biochemist
Sterility Devices Team
Office of Surgical and Infection Control Devices
Center for Devices and Radiological Health
Presentation Objectives

• Discussion of Industrial Ethylene Oxide (EtO) sterilization
  – Characteristics of EtO cycle
  – EtO sterilization cycle validation
Why EtO is used to sterilize Medical Devices?

- Broad material and device compatibility
  - Delicate devices sensitive to moisture or high temperatures
- Process flexibility
  - Adjustable parameters for load and device challenges
- Penetration through multiple layers of packaging.
  - Cartons and pallets vs. individual packages
- Large capacity facilities.
  - Small to very large (multiple pallet)
- Understood regulatory expectations
  - Long history of use and regulatory familiarity
Ethylene Oxide Sterilization Process Validation

• **Creation, definition and control of a Process that can provide sterile product.**
  – **Define Product:**
    • What is it?
    • How is it packaged and arranged?
    • How contaminated is it?

• **Characterize Equipment & Define Sterilization Process**
  – The equipment that will be used to sterilize the product and how will the process work
  – Explanation of the sterilization process and the equipment used to carry out the process.
  – Needs to be compatible with the intended product – device + packaging

• **Validation:**
  – Show the sterilization process works – can yield sterile product (process meets acceptable sterility assurance level)
  – Qualify sterilization site, equipment and process
    • Site, equipment and sterilization process all meet defined specification/tolerances.
    • Process can deliver acceptable lethality (kill/ destruction/deactivation of microorganisms)
Ethylene Oxide Sterilization Process Validation

• Creation, definition and control of a Process that can provide sterile product.
  – Define Product:
    • What is it?
    • How is it packaged and arranged?
    • How contaminated is it?

• Characterize Equipment & Define Sterilization Process
  – The equipment that will be used to sterilize the product and how will the process work
  – Explanation of the sterilization process and the equipment used to carry out the process.
  – Needs to be compatible with the intended product – device + packaging

• Validation:
  – Show the sterilization process works – can yield sterile product (process meets acceptable sterility assurance level)
  – Qualify sterilization site, equipment and process
    • Site, equipment and sterilization process all meet defined specification/tolerances.
    • Process can deliver acceptable lethality (kill/ destruction/deactivation of microorganisms)
\textbf{Ethylene Oxide Sterilization Process Validation}

- Creation, definition and control of a Process that can provide sterile product.
  - Define Product:
    - What is it?
    - How is it packaged and arranged?
    - How contaminated is it?

- Characterize Equipment & Define Sterilization Process
  - The equipment that will be used to sterilize the product and how will the process work
  - Explanation of the sterilization process and the equipment used to carry out the process.
  - Needs to be compatible with the intended product – device + packaging

- Validation:
  - Show the sterilization process works – can yield sterile product (process meets acceptable sterility assurance level)
  - Qualify sterilization site, equipment and process
    - Site, equipment and sterilization process all meet defined specification/tolerances.
    - Process can deliver acceptable lethality (kill/ destruction/deactivation of microorganisms)
Ethylene Oxide Sterilization Process

- **Preconditioning/Conditioning**
  - Aeration
  - Sterilization exposure/Dwell

- **Exposure/Dwell**
  - Load Humidity/Load Temperature
  - Pressure
  - Air Removal
  - Inert (N₂) overlay
  - Exposure/Dwell
  - EtO injection
  - Steam Injection
  - Vacuum and Nitrogen Flushing
  - Residual EtO

- **Safe threshold**

- Process phases that may contribute to EtO Emissions
Ethylene Oxide Process Validation Cont.

• Performance qualifications:
  – Microbiological – show sufficient lethality to extrapolate sterility assurance level for the process (10^-6, or probability of less than 1 in 1000000 positives after exposure to the intended sterilization cycle)
    • May be as high as conditions suitable to kill 1 million more spores after complete kill of organisms on validation loads.
    • Theoretical kill of up to 1 000 000 000 000 spores in worst case locations for a sterilization process.
  
  – Physical – show that the process parameters established to achieve sterilization in routine processing can consistently and reproducibly be met.
Ethylene Oxide Process Validation Cont.

• Routine monitoring and control
  – Systems to verify efficacy of routine processes
    • Parameter measurements
    • Biological indicators/ biological process challenge devices
    • Chemical indicators
  – Product Release
    • Decision making based on results from routine monitoring and control systems.
  – Maintaining Process effectiveness
Ethylene Oxide Process Validation Cont.

• Additional tests:
  – Sterilant residuals:
    • Ethylene Oxide and Ethylene Chlorohydrin residuals
  – Endotoxin/Pyrogen tests
  – Packaging
    • Transport/handling
    • Microbial barrier
Thank You!

Steve Elliott, Scientific Reviewer
Sterility Devices Team
Office of Surgical and Infection Control Devices
Center for Devices and Radiological Health
How FDA reviews sterilization information in premarket regulatory submissions for medical devices

Chris Dugard, Scientific Reviewer
Sterility Devices Team
Office of Surgical and Infection Control Devices
Center for Devices and Radiological Health
Industrial vs. Healthcare Sterilization

• Industrial sterilization
  – Typically used for terminally sterilized product
  – FDA regulates the process, not the sterilization facility
  – Inspections are conducted to ensure that process controls are in place and endpoints are reliably met

• Healthcare sterilization
  – Used for end-user sterilized or reusable devices in a healthcare setting
  – A healthcare sterilizer is considered a medical device
Submission and Review of Sterility Information in Premarket Notification (510(k)) Submissions for Devices Labeled as Sterile

Guidance for Industry and Food and Drug Administration Staff

• 3 categories
  – Established Category A (Steam, EO, radiation, dry heat, etc.)
    • Well-established methods with a long history of safe and effective use
    • FDA-recognized consensus standards can be used in review
  – Established Category B (H₂O₂, ozone, flexible chamber systems, etc.)
    • No recognized consensus standards, but have been previously evaluated
  – Non-traditional/alternative Sterilization methods
    • Little to no published information or history with FDA

Review of Sterilization in a Premarket Submission

• Terminal sterilization is considered part of the “manufacturing process”
  – Manufacturing is not reviewed in a 510(k), summary level sterility information only
  – Manufacturing controls reviewed for Class III devices, full validation reports required

• Healthcare sterilization utilizes FDA-cleared sterilizers
  – Requires review of full test reports
  – Additional requirements in “Reprocessing Medical Devices in Health Care Settings: Validation Methods and Labeling Guidance for Industry and Food and Drug Administration Staff” for reusable devices
Required Sterilization Information in a 510(k) for a Terminal Process

• Established A/B:
  – Description of the method
  – Description of sterilization chamber (if not rigid)
  – Sterilization site
  – Sterilant concentration and residuals (for chemical sterilants)
  – Sterilization dose (for radiation-based methods)
  – Validation method (e.g. half-cycle method) and standards followed
  – Sterility Assurance Level
  – Pyrogens (if applicable)
  – Description of sterile barrier and a summary of the methods used to support package integrity

• Non-traditional:
  – Full validation reports needed for review in addition to the information needed for established category A/B methods
Required Sterilization Information for Other Premarket Submissions

• IDE:
  – Validation data supporting device sterility throughout the investigational period needed

• PMA:
  – Manufacturing controls reviewed for Class III devices
  – Full validation reports required for review
Thank You!

Chris Dugard, Scientific Reviewer
Sterility Devices Team
Office of Surgical and Infection Control Devices
Center for Devices and Radiological Health