Sterility Assurance: Industry Viewpoint with Emphasis on Optimizing Ethylene Oxide Sterilization

Phil Cogdill
Technical Fellow
Senior Director of Quality, Sterilization and Microbiology
Medtronic
Presentation Key Points

- Sterilization starts and ends with the patient
  - Impacts manufacturing and distribution of devices across entire supply chain
- Sterilization is not just about eradicating microorganisms
  - Involves making sure it does not impact functionality or performance of devices across life cycle
- Ethylene Oxide (EO) sterilization is a highly controlled process
  - Used for sterilizing ~50% of medical devices worldwide
- New approaches may allow us to reduce amount of EO gas in industrial process
Utilizing the End-to-End (E2E) R&D Phase

STERILIZATION

Sterility Assurance End-to-End
E2E Sterility Assurance
R&D Phase

Product Design

Material Compatibility
(Product and Packaging)
2 Broad Categories of Sterilization Modalities

- Traditional – well-understood with developed standards
  - Ethylene Oxide
  - Moist / Dry Heat
  - Radiation – Gamma / E-Beam / X-ray

- Non-traditional – requires greater testing
  - Hydrogen Peroxide
  - NO₂ (Noxilizer™)
  - PAA (Revox™)
  - Chlorine Dioxide
Choosing Modality
1st Question is Material Compatibility

<table>
<thead>
<tr>
<th>Material</th>
<th>Radiation</th>
<th>Ethylene Oxide</th>
<th>Moist Heat</th>
<th>Dry Heat</th>
<th>VHP</th>
<th>Nitrogen Dioxide</th>
<th>ClO₂</th>
<th>PAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polycarbonate</td>
<td>Good - Excellent</td>
<td>Excellent</td>
<td>Not recommended</td>
<td>Up to 170°C</td>
<td>Excellent</td>
<td>Compatible</td>
<td>Compatible</td>
<td>Compatible</td>
</tr>
<tr>
<td>Polypropylene</td>
<td>Poor</td>
<td>Fair</td>
<td>Poor</td>
<td>Up to 135°C no stacking</td>
<td>Excellent</td>
<td>Compatible</td>
<td>Compatible</td>
<td>Compatible</td>
</tr>
<tr>
<td>Stainless steel</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Compatible</td>
<td>Excellent</td>
<td>Compatible</td>
<td>Compatible</td>
<td>Compatible</td>
</tr>
<tr>
<td>Nylon</td>
<td>Moderate</td>
<td>Very good</td>
<td>Very good</td>
<td>Marginal (120°C, unless heat stabilized up to 130°C)</td>
<td>Fair</td>
<td>Incompatible</td>
<td>Compatible</td>
<td>Compatible</td>
</tr>
<tr>
<td>ABS</td>
<td>Good</td>
<td>Excellent</td>
<td>Poor</td>
<td>No Data</td>
<td>Excellent</td>
<td>No data</td>
<td>Compatible</td>
<td>Compatible</td>
</tr>
<tr>
<td>Polyurethane</td>
<td>Excellent</td>
<td>Good - Poor</td>
<td>Not recommended</td>
<td>Varies on grade</td>
<td>Excellent</td>
<td>Incompatible</td>
<td>May Discolor</td>
<td>Compatible</td>
</tr>
<tr>
<td>Polyethylene</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Not recommended</td>
<td>Marginal up to 120°C</td>
<td>Excellent</td>
<td>Compatible</td>
<td>Compatible</td>
<td>Compatible</td>
</tr>
<tr>
<td>Polysulfide's</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Excellent</td>
<td>Up to 160°C</td>
<td>Excellent</td>
<td>Compatible</td>
<td>No Data</td>
<td>Compatible</td>
</tr>
<tr>
<td>Polyvinylchloride</td>
<td>Good</td>
<td>Excellent</td>
<td>Poor - Fair</td>
<td>Marginal up to 120°C</td>
<td>Excellent</td>
<td>Compatible</td>
<td>Compatible</td>
<td>Compatible</td>
</tr>
<tr>
<td>Common Sterile Pckg. Non-woven polyprop; Tyvek ® Mylar ®</td>
<td>Compatible</td>
<td>Compatible</td>
<td>Compatible</td>
<td>Marginal</td>
<td>Compatible</td>
<td>Compatible</td>
<td>Compatible</td>
<td></td>
</tr>
<tr>
<td>Cellulosic material Paper / Cardboard</td>
<td>Compatible</td>
<td>Compatible</td>
<td>Compatible</td>
<td>Incompatible</td>
<td>Incompatible</td>
<td>Incompatible</td>
<td>Absorbs but Compatible</td>
<td>Incompatible</td>
</tr>
</tbody>
</table>
E2E Sterility Assurance
R&D Phase

Product Design
Material Compatibility (Product & Packaging)
Validation Methodology
Sterilization Modality
E2E STERILITY ASSURANCE: Plan & Source Phase

- **Plan**
  - Identify where and how product will be produced and sterilized

- **Source**
  - Identify supplier of raw materials
  - Ensure raw material meets design specification and produced to ensure low bioburden
E2E STERILITY ASSURANCE:
Make Phase (i.e., Manufacturing)

- Environmental monitoring
- Sterile barrier (packaging)
- Change control
- Oversight for sterilization execution (e.g. terminal sterilization or aseptic processing)
- Sterilization validation maintenance
E2E STERILITY ASSURANCE: Sterilization Phase

- Receipt and shipment of products
- Inventory control
- Delivery of validated process
- Verification of process
- Quality review and approval process
- Release of product
E2E STERILITY ASSURANCE: Deliver Phase

- Assurance of sterile barrier (over shelf life)
- Environmental controls
  - Temperature
  - Humidity
EO – Same E2E Approach

- New Product Development / Life Cycle Management
  - Cycle Development
  - Cycle validation
  - Appropriateness of PCD
  - Material and Packaging Compatibility

- Assessment of EO Sterilization facility

- Sterilization Evaluation
  - Raw materials
  - Process components
  - Manufacturing aids

- Sterilization Execution
  - Internal / external
  - Monitoring of sterilization process
  - Follow ISO 10993-7

- EO Residual Management

- Standards for patient safety
## Benefits Unique to EO

<table>
<thead>
<tr>
<th>Mode</th>
<th>Variables</th>
<th>Advantages</th>
<th>Typical Use</th>
<th>Capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene oxide (EO)</td>
<td>Temperature, Humidity, Time, Gas concentration</td>
<td>Low temperature, High penetration, Adaptable process, Compatibility, Variable sized chambers (single cubic feet to 30+ pallets)</td>
<td>Temperature-sensitive products, Adhesive dressings, Tubing sets</td>
<td>Multiple locations, Global, In-house, Contract, Low spare capacity</td>
</tr>
</tbody>
</table>
EO Sterilization Process is Highly Controlled

1. Pre-conditioning
   Pre-conditioning Chambers

2. EO Processing
   Sterilization Chambers

3. Aeration
   Aeration Chambers
How Better Utilize EO
Modify Product Packaging

- Reduce paper materials in packaging and eliminate paper IFUs
  - Reduce amount of EO used and decrease EO residuals
- EO is absorbed in paper
- Move to electronic IFU
  - Same information with significantly less EO residuals
Optimized Process

- Conservative approach
  - High degree of confidence but requires large amounts of EO and higher emissions
- Optimized Cycles (BI/Bioburden)
  - Recognized by ANSI/AAMI
  - Shorter exposure times and lower EO levels
  - More complex
  - Will require time, validation and regulatory approval
## Reduce Exposure Time

<table>
<thead>
<tr>
<th>Equivalent Exposure Times</th>
<th>Resultant SAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>230 minutes (original production run data based on 120 minutes exposure timer setting)</td>
<td>$10^{-12.7}$</td>
</tr>
<tr>
<td>205 minutes (25 minutes less in exposure)</td>
<td>$10^{-10.6}$</td>
</tr>
<tr>
<td>195 minutes (35 minutes less in exposure)</td>
<td>$10^{-9.8}$</td>
</tr>
<tr>
<td>155 minutes (75 minutes less in exposure)</td>
<td>$10^{-6.5}$</td>
</tr>
</tbody>
</table>
Reduce Gas Concentration

Future Optimized Cycle

760 mg/l
670 mg/l
615 mg/l

390 mg/l
Consolidate Number of Cycles into Optimized Cycles

Currently validated cycles
- Cycle #1
- Cycle #2
- Cycle #3
- Cycle #5
- Cycle #7
- Cycle #8
- Cycle #10
- Cycle PC-A

Optimized
1 consolidated low-EO cycle (390 mg/L)
Multiple products
Summary

- EO sterilization processes are complex and lengthy
  - Each function in sterilization E2E approach is critical and can impact sterilization process and patient
- Sterilization involves more than eradicating microorganisms
  - Make sure functionality or performance is not impaired
- Few products sterilized by EO can move to other modalities
- Changes to sterilization processes are difficult and take time
  - Validation and testing over life-cycle of product
  - Non-traditional methods do not have nationally recognized standards
- Potential approaches to better utilize EO but all will require time