Introduction to Ethylene Oxide Sterilization and Regulatory Updates

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Agenda

• Regulatory overview
• Ethylene Oxide Sterilization
• Process Definition
• Performance Qualification
Regulatory overview
Sterilization Methods

**Ethylene Oxide**
- (EO) gas

**Radiation**
- Gamma ray
- Accelerated electrons
- X-rays

**Other**
- Moist heat
- Dry heat
- Vaporized hydrogen peroxide
- Gas plasma
- LTSF

**Most common methods**
for terminal sterilization of single use medical devices
ISO11135:1994 – Sterilization of health care products – Ethylene Oxide
Requirements for development, validation and routine control of a sterilization process for medical devices. (Also contained Guidance section)

ISO11135-1:2007 – Sterilization of health care products – Ethylene Oxide
Requirements plus limited Guidance section

Guidance on the application of ISO11135-1

ISO11135:2014 – Sterilization of health care products – Ethylene Oxide
Requirements for development, validation and routine control of a sterilization process for medical devices. (Also contains comprehensive Guidance section)

3-year transition period lasted until July 2017; Transition period is now closed
# Relevant Standards

## EO Sterilization and Validation

**ISO 11135:2014**  
Sterilization of medical devices – Requirements for the development; validation and routine Control of a Sterilization Process for Medical Devices – Ethylene Oxide

## EO Residuals

**ISO 10993-7:2008 (R) 2012**  
Biological evaluation of medical devices - Part 7: Ethylene oxide sterilization residuals

## Bacterial Endotoxin Test (LAL)

- *United States Pharmacopeia* (USP) Chapter <85>  
  Bacterial Endotoxins Test
- *Japanese Pharmacopeia* (JP) Chapter 4.01 Bacterial Endotoxins Test
- *ANSI/AAMI ST72 : 2011 (R) 2016 – Bacterial Endotoxins
- *New draft document DIS11737-3 in progress*

## Bioburden

**ISO 11737-1:2018**  
Sterilization of medical devices (Microbiological methods) Part 1: Determination of a population of microorganisms on products
### Relevant Standards

#### Product Sterility

- **ISO 11737-2:2009 (R) 2014**  
  Sterilization of medical devices (Microbiological methods) Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process
- **United States Pharmacopeia (USP) Chapter <71>** Sterility Tests
- **European Pharmacopeia (EP) Chapter 2.6.1 Sterility**
- **Japanese Pharmacopeia (JP) Chapter 54. Sterility Test**

#### Biological Indicator Tests

- **ISO 11138-1:2017**  
  Sterilization of health care products (Biological indicators) Part 1: General requirements
- **ISO 11138-2:2017**  
  Sterilization of health care products (Biological indicators) Part 2: Biological indicators for ethylene oxide sterilization processes
- **ISO 14161: 2009 (R) 2014**  
  Biological indicators. Guidance for the selection, use and interpretation of results

#### Quality Systems

- **ISO 13485: 2016**  
  Medical Devices, Quality Management Systems
Ethylene Oxide Sterilization
## Ethylene Oxide – History

<table>
<thead>
<tr>
<th>Event</th>
<th>Year</th>
<th>Responsible Party</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethylene Oxide discovered</td>
<td>1859</td>
<td>Charles Wurz</td>
</tr>
<tr>
<td>First production of Ethylene Oxide</td>
<td>1925</td>
<td>Union Carbide Chemicals</td>
</tr>
<tr>
<td>Patent for sterilization of spices</td>
<td>1938</td>
<td>Lloyd Hall</td>
</tr>
<tr>
<td>Use in sterilization of materials</td>
<td>1940</td>
<td></td>
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</tbody>
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Dr. Lloyd Augustus Hall, a food scientist (and a Northwestern University classmate of Carroll L. Griffith), while working for Griffith Laboratories, devised a process known as the Ethylene Oxide Vacugas treatment to control the growth of molds and bacteria. Griffith and Hall received US Patent 2,189,949 in 1940.
Ethylene Oxide

Properties

• Toxic gas
• “Sweet smell” from ca. 500 ppm concentration
• Forms with air explosive mixtures (2.6 %)
• Oncogenic by inhalation
• Irritating for skin and respiratory system
• Mutagenic for animals and very likely for humans
Ethylene Oxide

Mode of Action

• Extremely reactive

• Irreversible reaction with DNA and proteins (alkylation)
  o The molecule loses function
  o Replication stops
  o The cell dies
Ethylene Oxide Sterilization

Most commonly used industrial method for medical devices, mainly used to sterilize:

• Heat-sensitive material
  o Products that cannot tolerate the high temperatures of Moist Heat (Steam) Sterilization

• Material sensitive to ionizing radiation
  o Products can embrittle and discolor over time after exposure to γ, E-beam, X-ray
Device/packaging must be permeable to the gas (Be careful with tight-end valves, 3 way stopcocks, pouches, etc)

- No aqueous substances
- No protein-type materials
- Powders, batteries, electronic circuits have to be assessed (risk of explosion)
- Vacuum/heat can have adverse impact on some packaging (bubble wrap packaging, polystyrene)
Critical Parameters for Effective EO Treatment

- EO Concentration
- Relative Humidity
- Temperature
- EtO Dwell Time

Deactivation of Microorganisms

Confidential
Temperature (T)

**EtO kills microorganisms**
even at temperatures below 10°C (50°F)

**Industrial sterilization**
performed in 40-60 °C
(104–140°F) temperature range

**Q10 Effect**
increase by 10°C
(18°F)
= 2x Deactivation Rate

**Temperature increase**
may increase of permeability of gases through materials
Relative Humidity (RH)

Necessary for alkylation reaction

Relative humidity may assist penetration of EO through materials

EO is most effective at RH > 30%
At constant T and RH – if EO concentration increases microbiological Deactivation is more effective - up to c. 800 mg/l

- ~ 500 mg/L @ 131°F
- ~ 800 mg/L @ 86°F
Time

Microbiological deactivation is more effective with longer gas dwell phase.

Industry cycles
2 to 10 hours gas dwell phase
Typically 3-4 hours
Sterilization Process

The sterilization process has 3 key phases:

1. **Preconditioning**
2. **Chamber cycle**
3. **Aeration**
Preconditioning, typically:

- 35–45 °C
- 45–75 %RH
Typical EO Cycle Design – Deep Vacuum

**GENERIC CYCLE**

- **Leak test**
- **Initial vacuum**
- **Inertization**
- **Steam injection and conditioning**
- **Gas injection**
- **Gas evacuation**
- **Gas washes: first nitrogen and then air**
- **Release to atmospheric pressure**
Aeration

- Aeration, typically:
  - 35 – 50 °C
  - Forced circulation
Monitoring EO Sterilization Processes
• Usually, the BI contains at least a million spores of an organism that is highly-resistant to the EO process.

• The name of the bacterium is commonly *Bacillus subtilis* or *B. subtilis*.
  o It has been renamed and is officially *B. atrophaeus*.
Biological Indicators (BI)

• >$10^6$ Spores of resistant strain *Bacillus atrophaeus*

• Can come in many different designs
Monitoring EO Sterilization - Biological Indicators

Negative: No Growth

Positive: Growth

Morphology

BIs in vial with Medium
We design the validation to show that the BI is more difficult to kill than natural occurring bioburden (microorganisms in or on product).

**EO effective against wide range of organisms**

- E. coli
- Salmonella
- Strep
- Viruses
- Molds
Process Definition
**Process Definition**


- **Section 8.3**
  - Performed in development sterilizer or routine sterilizer.

- **Section 8.6**
  - BIs used:
    - Shall be at least as resistant as product bioburden
    - Be placed at worst case device locations, or placed within PCD.
Customer Needs To Define

- Product Families/Processing Categories
- Finalize Packaging
- Load Configuration
- Bioburden
- Internal PCD
Customer Needs To Define

Product Families

• Products shall be grouped into Families (collection of products determined to be similar)

• Within a family, product representing “worst case sterilization challenge” may be selected as Internal PCD and used to evaluate the delivered lethality by the process
Customer Needs To Define

Product Families

- Different product families can be included in a common EO cycle (e.g. processing category) even if families are dissimilar in the details
- If including multiple Product Families in the same EO cycle, then most resistant internal PCD among all families should be used to ultimately develop the cycle
Finalize Packaging and Load Configuration

- Finalize Packaging
  - Prototype Design is not advised

- Product packaging includes;
  - Corrugate, box thickness
  - Pouching materials (Tyvek)
  - Single, Double pouching.
  - Packing count (quantity/box)

- Load Configuration
  - Stacking pattern of shippers on the pallet
  - Density of load
  - Securing products on the pallet (e.g. Banding, wrapping)
Process Challenge Device (PCD)

Item designed to constitute a defined resistance to the sterilization process and used to assess performance of the process

- Internal PCD (IPCD)
- External PCD (EPCD)
- Master PCD (MPCD)
Customer Needs To Define

Internal PCD

BI disc in grommet
Overview of External PCD

External Process Challenge Devices
Also known as:

- EPCDs
- Test Packs

Here is an example of a processed pallet (arrow shows External PCD)
Next Steps

Design Proposed cycle parameters

Use design inputs gathered from customer
Fractional Runs

ANSI/AAMI/ISO 11135:2014, section 8.6

Also known as ‘sublethal’

“Process in which exposure time is reduced compared to that specified in the sterilization process”
Fractional Runs

During execution of Fractional Runs

• Appropriateness of BI vs Bioburden [NPRT]
• Cycle Development
• Definition of IPCD
• Comparison of IPCD’s
• Relative Resistance Test Pack Development  [IPCD v EPCD]
Fractional Runs

Hierarchy required

- External PCD
- Internal PCD
- Product Bioburden

Sterilization Resistance
Fractional Runs

Define Half Cycle Gas Dwell Time

- Provide full kill of Internal PCD
- You can allow BI positive in the External PCD during the Half-Cycle but Half-Cycle dwell time must not be too short where External PCD positives can occur in projected Full-Cycle (routine processing)
Fractional Runs

$D_{10}$ Value

Time required to achieve inactivation of 90% of a population of the test microorganism under stated conditions

- 90% reduction = 1 log$_{10}$ reduction
Sterility Assurance Level (SAL)

- Probability of a single viable microorganism occurring on an item after sterilization

Is a quantitative value, generally $10^{-6}$

- A probability of less than one-in-million
Validation of an EO cycle

Performance Qualification
Performance Qualification

ISO 11135:2014

• PQ consists of both microbiological and physical performance qualification and is performed in the equipment used to sterilize the product
  o Microbiological Performance Qualification (MPQ) and
  o Physical Performance Qualification (PPQ)

• Operationally these are referred to as the half and the full cycles, respectively
Compared to the normal type of cycle that you will run in routine production, the “Half cycle” uses one-half of the EO gas exposure time.

- **Routine cycle**: 4 hours of gas exposure
- **Half cycle**: 2 hours of gas exposure
Why do we run a Half cycle?

To confirm BI lethality

Demonstrate total inactivation of a $10^6$ BI at a Half-cycle exposure time. When exposure time is doubled, a minimum 12 SLR is delivered during a Full-cycle EO exposure.
“A typical performance qualification requires three consecutive successful validation cycles to demonstrate reproducibility the first time the cycle is validated. The first successful cycle indicates that the proposed cycle lethality is achievable. The second successful cycle indicates that the cycle can be repeated successfully, while the third demonstrates reproducibility.”
Half Cycles

• Preconditioning time should be less than routine (full cycle) time

• Chamber settings should be sub-nominal for at least one parameter (worst-case)
  o Temperature
  o Humidity
  o Pressure / Gas Concentration
  o Time (Gas Exposure)
Half Cycles

• Run Half Cycles using the parameters established during Cycle Development.

• Place BI samples and sensors according to the protocol

• The number of Biological Indicators and temperature/humidity sensors required is defined in ISO 11135:2014
Full Cycles

- Run three Full Cycles using parameters which will represent routine processing
- Place samples and sensors according to the protocol
- Full Cycles will evaluate:
  - Aeration/EO Residues
  - Product functionality/package integrity
  - At least 1 cycle should contain sensors
• Aeration Requirements/EO Residues
  ○ Develop dissipation curve to establish release time

• Qualify release time based on three (3) separate cycles

• Allowable residue limits are based on intended use of product
Summary

- Regulatory overview
  - Many Standards involved. Several have been recently updated.

- Ethylene Oxide Sterilization
  - How the EO process works

- Process Definition
  - How to define your sterilization process

- Performance Qualification
  - How to validate your sterilization process
  - Confirmation of Sterility Assurance Level
Thanks for listening