Qualification of Ethylene Oxide and Gamma Sterilisation Processes

Daniel Lanzon
Microbiology Manager

Pfizer Perth
• Overview for the Qualification
  – Ethylene Oxide (EtO) sterilisation process
  – Gamma sterilisation process
EtO Sterilisation

- Market required the vial surface of a product to be sterile for theatre use
- Parenteral product terminally sterilised
- Packaged into a theatre packet
- EtO selected to sterilise the vial surfaces
EtO Sterilisation

• EtO commonly used to sterilize objects sensitive to temperatures or radiation
• EtO penetrates well, moving through paper, tyvek, and some plastic films.
• EtO gas is highly flammable, toxic and carcinogenic.
• Bactericidal and sporicidal activity is achieved by reaction of EtO with nucleic acid.
EtO Sterilisation

Typical EtO treatment conditions:

- Temperature between 30 °C and 60 °C
- Relative humidity above 30%
- Gas concentration between 200 and 1000 mg/L
- Exposure time of 2 to 10 hours
EtO Processing steps

- **Preconditioning/conditioning**
  - Precondition to a specified RH and temperature

- **Sterilization cycle**
  - Exposure to EtO gas

- **Aeration**
  - Dissipation of remaining gases
Cycle Development

- Equipment/Process qualified by contract steriliser
  - IQ/OQ/PQ completed
  - SOPs in place (Operational, Change control, maintenance etc)
  - PM/calibration program in place

- Sterilisation cycle development
  - Identify Load pattern
  - Define preconditioning
  - Define sterilisation cycle
  - Define sterilisation requirements e.g. SAL of $10^{-6}$
  - Define product attributes to be tested

*Use Contract Steriliser experience in developing the sterilisation process*
Sterilisation Load Pattern

- Developed maximum load pattern
  - Number of shippers
  - Stacking orientation
  - Load orientation (preconditioning/cycle)
  - Number of pallets
  - Mixed load or dedicated load
EtO Qualification Example

- Pilot batch used to provide confidence in the proposed process
- Pilot batch manufactured and exposed through the EtO sterilisation process
  - proposed preconditioning and full cycle
- Challenged with:
  - Biological Indicators
  - Temperature and relative humidity data loggers
  - Container closure
Steps in EtO qualification

- Qualification process established
  - Packaging bioburden
  - Load preconditioning
  - Survival Cycle
  - Half Cycle
    - Support Overkill sterilisation to provide SAL $10^{-6}$
  - Full Cycle
    - Support container closure of theatre packet
    - Support container closure of vial
    - Removal of Ethylene oxide residuals or byproducts
    - Product stability over shelf life
    - Sterility
    - Multiple sterilisation

- Revalidation requirements
Packaging bioburden

- Product packaged in Perth shipped to Melbourne for sterilisation
- Starting material bioburden controlled
- Packaging process controlled
- Bioburden monitored throughout the process (not exposing to the sterilisation process)
• Bioburden determined of the product as per ISO 11737-1:2006
  
  – Understand your product
  – Bioburden recovery method qualified
  – Is a correction factor required to compensate for incomplete removal of micro-organisms from the product?

• Bioburden Determined across multiple batches demonstrated a consistent low bioburden
Load Preconditioning

• Use specified load pattern
• Demonstrate temperature and relative humidity distribution throughout the load
• Time set based on equilibrium time
• Simulate winter conditions
Microbial Challenge (BIs)

- Self contained BIs used (*Bacillus atrophaeus* worse BIs for EtO)
- Number BIs determined as per ANSI/AAMI/ISO 11135-1:2007
- 50 BIs located throughout the load (ensuring worse case locations captured)
- BIs exposed to complete process
- Positive control BIs exposed to complete process except for the sterilisation cycle exposure
Survival cycle

• Demonstrate capability to recover BIs

• Survival cycle identical as full cycle except the EtO gas exposure time is less
  – Mindful of selection of exposure time

• Single cycle

• Survivors support recovery process
Half Cycle

- Half cycle identical as full cycle except the EtO gas exposure time is half

- Run in triplicate

- Challenges
  - Bioburden
  - Bls
  - Sterility

- Half cycle used to support a SAL of $10^{-6}$
**Full cycle**

- **Full Cycle** Primarily used to support product and packaging integrity

- **Run in triplicate**

- **Challenges**
  - Bioburden
  - BIs
  - Sterility
  - Container closure of theatre packet
  - Container closure of vial
  - Ethylene Oxide residual
  - Product Stability
Resterilisation

- Samples exposed to multiple cycles at worse case locations

- Challenges
  - Container closure of theater packet
  - Container closure of vial
  - Ethylene Oxide residual
  - Product Stability
Revalidation/requalification

• Re-qualification program established
  – E.g. annual half and full cycle

• Change Control
  – Any change to the EtO sterilisation process that could effect the effectiveness of the EtO gas
    • New chamber/chamber modification
    • Type of gas
    • Preconditioning change
    • Recipe change
  – Product change
    • Bioburden change
    • Packaging change
    • Component Change
    • Load change
Revalidation/requalification

Asses All changes for impact to your product
Routine Processes

• Contract sterilisers/manufactures responsibilities
  – Defined in a Robust Quality Agreement
  – SOPs defining requirements
  – Manufacturer responsible for the SAL of the product

• What are the critical parameters
  – Defined in a SOP
  – Used as a release criteria

• Do you use BIs??
• Market required a sterile hospital grade disinfectant
• Product filled into a bottle/spray mechanism and packaged within a low-density polyethylene (LDPE) bag
• Product terminally sterilised via gamma irradiation
Gamma Irradiation
Mode of Activity

- Bacteria, spores and viruses are destroyed by radiolysis

- High energy emitted from an Isotope source (e.g. Cobalt 60) breaks chemical bonds in DNA and other cell structures that lead to dysfunction and destruction of the microbe.
Qualification process

- Cycle development
- Product bioburden
- Dose established and verification
- Performance Qualification
  - Dosimetry
  - Container closure
  - Product stability over shelf life
  - Sterility
  - Maximum dose exposure

- Requalification/Revalidation/Change Control
Cycle development

• Developed maximum load pattern
  – Number of shippers per tote bin
  – Load orientation
  – Product density

• Contractor expertise used to determine cycle exposure
Packaging bioburden

- Product packaged in Perth shipped to Melbourne for sterilisation
- Packaging process controlled
- Starting material bioburden controlled
- Bioburden monitored throughout the process (not exposing to the sterilisation process)
- Demonstrated robust microbial control
• Bioburden determined of the product and device as per ISO 11737-1:2006
  – Understand your product
  – Bioburden recovery method qualified
  – Is a correction factor required to compensate for incomplete removal of micro-organisms from the product?
  – The whole device, including product is evaluated for bioburden

• Determined across multiple batches
Dose establishment and verification


- Sterilization dose: Minimum dose required to achieve the specified SAL

- What is the sterilisation dose that will be established
  - 25 kGy/15 kGy/Other
  - Single or multiple batches used for qualification

- Which method will be used to substantiate the dose
  - Method 1
  - Method 2
  - Method $V_{D_{\text{max}}}^{25}$ or Method $V_{D_{\text{max}}}^{15}$
Dose Establishment and verification \(V_{D\text{max}}^{25}\)

- Average bioburden determined from 3 batches
- Dose that provides a SAL of \(10^{-2}\) is determined from Table 9 in ISO 11137-2. This is the verification dose

Table 9 extract from ANSI/AAMI/ISO 11137-2:2012 Sterilization of health care products — Radiation — Part 2: Establishing the sterilization dose

<table>
<thead>
<tr>
<th>Average bioburden</th>
<th>SIP equal to 1.0 (V_{D\text{max}}^{25}) (kGy)</th>
<th>SIP dose reduction factor (kGy)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>7.2</td>
<td>3.55</td>
</tr>
<tr>
<td>12</td>
<td>7.3</td>
<td>3.53</td>
</tr>
<tr>
<td>13</td>
<td>7.4</td>
<td>3.51</td>
</tr>
<tr>
<td>14</td>
<td>7.5</td>
<td>3.50</td>
</tr>
<tr>
<td>15</td>
<td>7.6</td>
<td>3.48</td>
</tr>
<tr>
<td>16</td>
<td>7.6</td>
<td>3.47</td>
</tr>
<tr>
<td>17</td>
<td>7.7</td>
<td>3.46</td>
</tr>
</tbody>
</table>
Dose Establishment and verification \( VD_{\text{max}} 25 \)

- 10 items exposed to the selected verification dose
- Actual dose must be not exceed the verification dose by > 10%
- All product is individually sterility tested
- If not more than 1 positive sterility test then verification accepted and 25kGy substantiated to achieve the required SAL \((10^{-6})\)
Performance Qualification

• Multiple dosimeters per shipper
• At different stages of the sterilisation train (beginning, middle and end)
• Triplicate exposure
  – Dosimetry
  – Sterility
• Selection routine dosimeter location
• Setting a maximum dose
  – Product stability over shelf life
  – Container closure
Dose Audit

- Periodic sterilisation dose audits are carried out to confirm the continued appropriateness of the sterilisation dose
- Average bioburden determined from 1 batch
- 10 items exposed to the verification dose used in the initial qualification
- Actual dose must be not exceed the verification dose by > 10%
- All product is individually sterility tested
- If not more than 1 positive sterility test then sterilization dose audit is accepted.
Revalidation/Requalification

• Re-qualification program established
  – E.g. annual repeat of dosimetry studies
  – Dose audit (quarterly)

• Change Control
  – Any change to the radiator that could effect the dose distribution or dose must be assessed
    • Delivery system change
    • Source cable replacement
  – Cobalt source replenishment
  – Product change
    • Density change
    • Bioburden change
    • Packaging change
    • Component change
Useful References

- AAMI TIR33:2005 Sterilization of health care products - Radiation sterilization - Substantiation of a selected sterilization dose - Method VDmax
Useful References

- AAMI TIR14:2009 Association for the Advancement of Medical Instrumentation **Contract sterilization using ethylene oxide**
- AAMI TIR28:2009 Association for the Advancement of Medical Instrumentation **Product adoption and process equivalence for ethylene oxide sterilization**
- AAMI TIR16:2009 Association for the Advancement of Medical Instrumentation **Microbiological aspects of ethylene oxide sterilization.**
- AAMI TIR15:2009 Association for the Advancement of Medical Instrumentation **Physical aspects of ethylene oxide sterilization**
Questions