Qualification of Ethylene Oxide and Gamma Sterilisation Processes

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Presentation Outline

- **Overview for the Qualification**
  - Ethylene Oxide (EtO) sterilisation process
  - Gamma sterilisation process

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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**

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EtO Processing steps

- **Preconditioning/conditioning**
  - Precondition to a specified RH and temperature
- **Sterilization cycle**
  - Exposure to EtO gas
- **Aeration**
  - Dissipation of remaining gases

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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 determination

- **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

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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
  - BIs
  - 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

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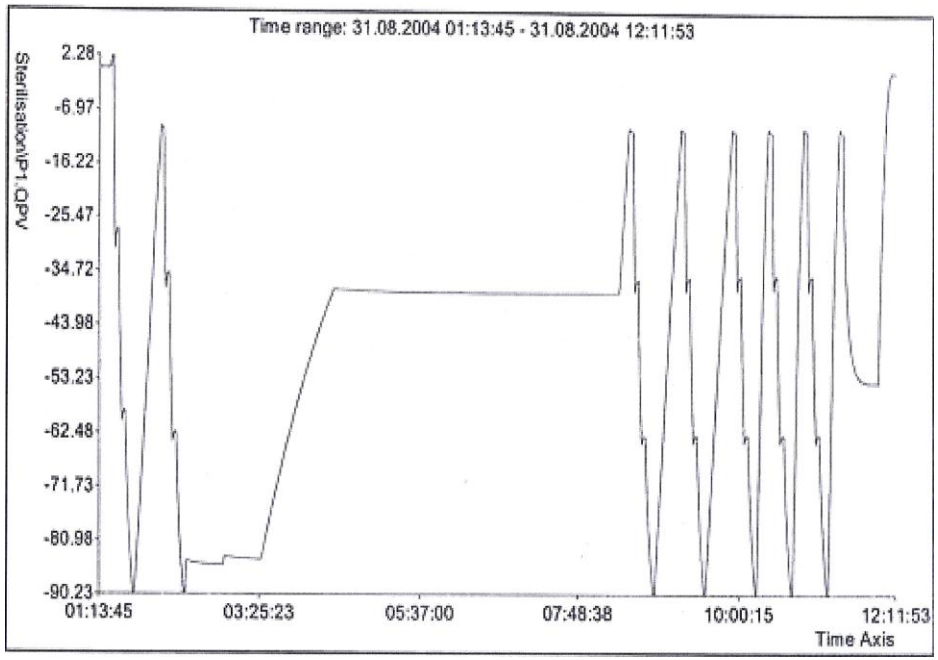
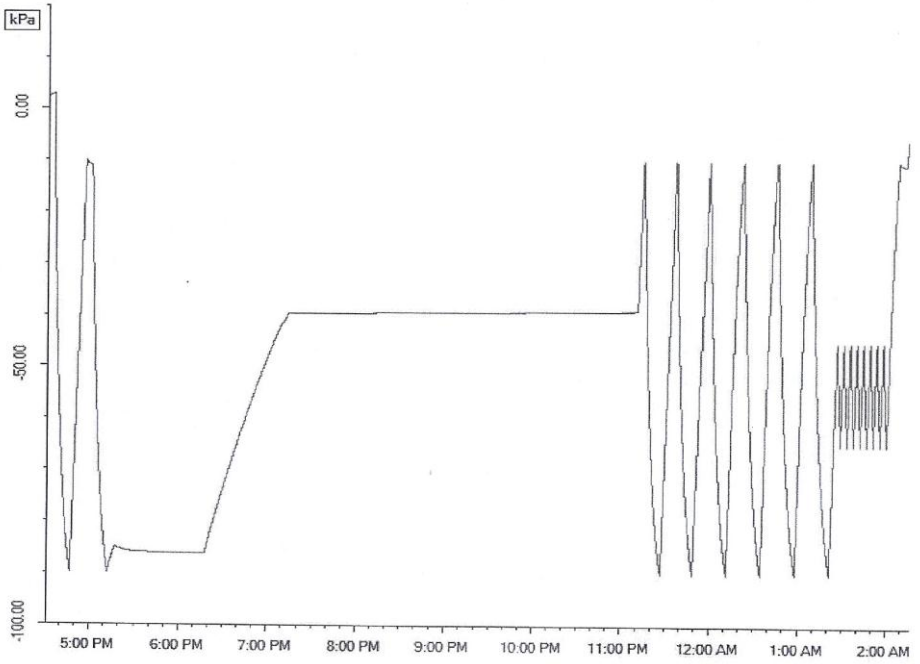
Revalidation/requalification

- **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??**

Gamma Sterilisation

- 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 determination

- **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

- **ISO 11137-2 2012 Sterilization of healthcare products – radiation – Part 2: Establishing the sterilization dose.**
- **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 $VD_{max}25$ or Method $VD_{max}15$

Dose Establishment and verification $VD_{max}25$

- **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

Average bioburden	**SIP equal to 1.0** $VD_{max\ 25}$ (kGy)	**SIP dose reduction factor** (kGy)
11	7.2	3.55
12	7.3	3.53
13	7.4	3.51
14	7.5	3.50
15	7.6	3.48
16	7.6	3.47
17	7.7	3.46

Dose Establishment and verification $VD_{max}25$

- 10 items exposed to the selected verification dose
- Actual dose must be not exceed the verification doe 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

- ANSI/AAMI/ISO 11137-1-2006/(R)2010 Sterilization of health care products - Radiation - Part 1: Requirements for the development, validation and routine control of a sterilization process for medical devices
- ANSI/AAMI/ISO 11137-2-2012 Sterilization of health care products - Radiation - Part 2: Establishing the sterilization dose.
- ANSI/AAMI/ISO 11137-3-2006(R)2010 Sterilization of health care products - Radiation - Part 3: Guidance on dosimetric aspects
- AAMI TIR33:2005 Sterilization of health care products - Radiation sterilization - Substantiation of a selected sterilization dose - Method VDmax
- AAMI TIR40:2009 Sterilization of health care products - Radiation - Guidance on dose setting utilizing a Modified Method 2.
- ANSI/AAMI/ISO 11737-1-2006 Sterilization of health care products – Microbiological Methods - Part 1: Determination of the population of microorganisms on product.

Useful References

- **AAMI TIR14:2009** Association for the Advancement of Medical Instrumentation **Contract sterilization using ethylene oxide**
- **ANSI/AAMI/ISO TIR11135-2:2008**Association for the Advancement of Medical Instrumentation **Sterilization of health care products — Ethylene oxide — Part 2: Guidance on the application of ANSI/AAMI/ISO 11135-1**
- **ANSI/AAMI/ISO 11135-1:2007 Sterilization of health care products — Ethylene oxide — Part 1: Requirements for development, validation, and routine control of a sterilization process for medical devices**
- **ANSI/AAMI/ISO 11138-2:2006/(R)2010 Sterilization of health care products - Biological indicators - Part 2: Biological indicators for ethylene oxide sterilization processes.**
- **AAMI TIR28:2009** Association for the Advancement of Medical Instrumentation **Product adoption and process equivalence for ethylene oxide sterilization**
- **ANSI/AAMI/ISO 10993-7:2008 Biological evaluation of medical devices—Part 7: Ethylene oxide sterilization residuals**
- **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