STERILIZATION STRUGGLES: IDENTIFYING THE BEST PROCESS FOR YOUR PROJECT

Darci Diage Ward

STERILE

Free of viable microorganisms

Sterility assurance level of 10^{-6}

No contamination

Prevent infection

Ensure safety

TYPES OF STERILIZATION

- Steam (autoclave)
- Ethylene oxide
- Radiation – Gamma, E-beam and X-ray
- Hydrogen peroxide
- Nitrogen dioxide
- Liquid chemical

STEAM STERILIZATION

- Autoclaving = steam, pressure, temperature and time
- Uses high temperature to break down cell walls and water to effectively kill microbes (including spores)
- Extremely effective for heat stable liquids, instruments, glassware and vials
- Typical cycle is 121^{oC} for 30 minutes and optional dry time
- Capital equipment is required to process internally and service providers that offer routine autoclaving to a validated cycle are limited

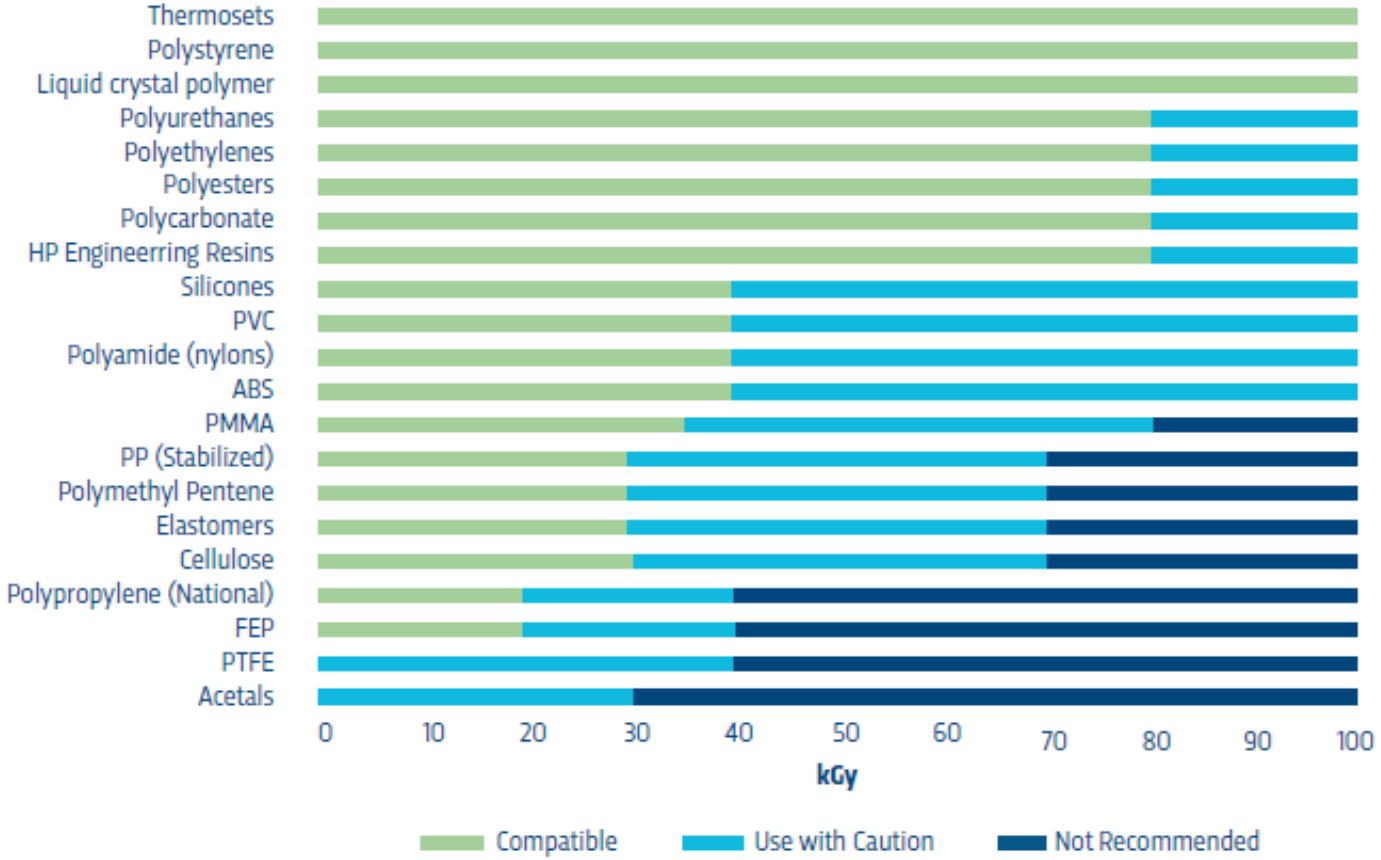
ETHYLENE OXIDE

- ETO = gas concentration, temperature, relative humidity and time
- ETO gas penetrates the cell to the DNA level and kills the microbe with alkylation
- Typical cycle uses 450 mg/l at 63°C with a relative humidity of 80% and exposure time of 4 hours
- Excellent for catheters, implantable pulse generators, stents, grafts and combination products
- Disadvantages associated with ETO are the lengthy cycle time, the cost, potential hazards to personnel and risk of cancer to excessive emissions

RADIATION

- Uses various sources of radiation (electrons, emitted photons)
- Cobalt self-disintegrates emitting photons or x-ray generated photons that collide with electrons or electrons colliding with electrons that essentially breaks the DNA preventing replication
- Extremely effective for liquids, catheters, syringes, needles, plastics. metals and high density products depending on the radiation source
- Typical processing is 25kGy (limited by natural bioburden)
- Material compatibility

RADIATION MATERIAL COMPATIBILITY



OTHER METHODS

Hydrogen peroxide

- Low temperature and used for prefilled syringes and instruments
- Low ingress so does not permeate into lumens well

Nitrogen Dioxide

- Low temperature and used for prefilled syringes
- No ingress

Liquid Chemical

- Room temperature and used for tissue and reprocessed devices
- Needs mechanical pumping to push into lumens

STERILIZATION PROCESSES IN A NUT SHELL

ETHYLENE OXIDE PROCESSING

Preconditioning – 24 hours

- Required to condition the load for exposure climate

Exposure – 12 hours

- Actual gas exposure is typically 4 hours; however, total cycle time can be 12 hours for vacuum to remove air from the product and replace with gas

Aeration – 24 hours

- Required to off-gas the product load to reduce residuals to non-toxic levels

Total Cycle Time = 60 hours

Product Release Activities:

- Biological indicator sterility test – 7 days
- Endotoxin test – 2 days

ETHYLENE OXIDE CONSIDERATIONS

Vacuum and nitrogen are required during processing to remove air from the chamber

- EO is toxic, flammable and explosive; the explosive limits are 2,6 % to 100 % EO by volume in air – total air removal is required prior to injection
- Ensure materials are compatible with physical insults of processing

Requires open-ended pathways

- Gas needs to permeate through materials or ingress into lumens – don't design with a potted joints and long lumens take longer to sterilize

Packaging needs to be permeable to gas and withstand vacuum

RADIATION PROCESSING

Shippers are received at the sterilizer and weighed to verify the validated configuration

- Won't process if weight of shipper is higher or lower than 10%

Placed in the rack or tote on the conveyor

- Can process 1 shipper or 1000 shippers – there's no load configuration

Exposed to sterilizing radiation in a matter of minutes to a few hours

Total Cycle Time = 24 hours

Product Release Activities:

- Reference dosimeter verifies targe dose range was met
- Certificate of irradiation is issued

RADIATION PROCESSING

- Dose rate
  - X-ray
  - E-beam
  - Gamma
- Penetration
  - X-ray
  - Gamma
  - E-beam
- Packaging
  - Gamma
  - X-ray
  - E-beam
- Material Compatibility
  - Gamma
  - X-ray
  - E-beam

RADIATION PROCESSING CONSIDERATIONS - GAMMA

Sterilization dose is based on the natural bioburden of the device

- Once the dose range is established the materials can't be changed

Material compatibility is critical

- Photons break apart DNA so a lower dose can be used

Deep penetration and low-dose rates due to self-disintegration of Cobalt-60 and Cesium-45

- Can process various box and packaging configuration in the same tote

Gamma resistant organisms can develop

RADIATION PROCESSING CONSIDERATIONS - EBEAM

Sterilization dose is based on the natural bioburden of the device

- Once the dose range is established the materials can't be changed

Material compatibility is critical

- Electrons emit energy that is absorbed and cross-links bonds
- Can be used to modify polymers but can also break down polymers

Configuration of product within the shipper is a consideration

- Metal components can enhance the beam in high dose distribution throughout the shipper
- Glass can diminish the beam resulting in low dose distribution

Due to the rack used to move the product on the conveyor there are limitation in shipper size

STERILIZATION COSTS

ETHYLENE OXIDE

Validation Budget = $45,000

- Develop a biological indicator
- Fractional cycle to verify product sterility < BI sterility
- 3 half cycles to verify total BI kill
- Full cycle to test product for EO residuals

Routine Processing = $4,000

EBEAM RADIATION

Validation Budget = $20,000

- Bioburden on 3 separate lots of product to determine verification dose
- Single layer dose map
- Verification dose on 1 lot to confirm product sterility
- Dose map of routine shipper

Routine Processing = $1000 (dependent on # of boxes)

ETHYLENE OXIDE INDIRECT COSTS

- Load configuration – predict the maximum load needed with the reality of cost
- When planning for validation, need to procure packaging to build out the maximum load
- Shipping costs
- Product samples for validation = 45 units (approximately)
- Laboratory fees for validation
- Laboratory fees for routine processing
- Save ALL materials during development to be used in validation

RADIATION INDIRECT COSTS

- Product placement in packaging in shipper can't change
- Manufacturing processes can't change
- Shipping costs
- Laboratory fees for validation
- Laboratory fees for routine processing
- Product samples for validation = 48 units
- Need finished devices to validate

STERILIZATION MAINTENANCE COSTS

ETHYLENE OXIDE

Annual Re-validation

- Required to be performed each year a load is processed
- Performed to a released protocol
- Permitted to perform document review for 2 years in a row
- A microbiological revalidation (MPQ) is required every 3rd year
- Costs can vary for outside expert to review or internal resource who is skilled and qualified
- MPQ requires half + full cycle data

EBEAM RADIATION

Quarterly Dose Audits

- Required each quarter of the year that a run is processed
- Performed to a released protocol
- Requires 20 devices – can be rejected units representative of final device
  - 10 for bioburden testing
  - 10 for verification dose sterility test
- Costs for lab fees and verification dose

PERSONAL PITFALLS

PRODUCT DEVELOPMENT

EXCELLENT IDEA!	SELECT PACKAGING	STERILIZATION	BIOCOMPATIBLITY	VERIFICATION/ VALIDATION
Select materials and verify feasibility	Compatible with the proposed sterilization method	Initiate validation	Required for any invasive and non-invasive device	In parallel with biocompatibility testing

PROJECTS IMPACTED.....

Ethylene Oxide Dunnage

- Packaging, fake product and shipping can be shockingly expensive
- Initial load is too small and you outgrow the validated process and need to revalidate

E-beam Sterilization Packaging Configuration

- Stacking shelf cartons vertically vs. horizontally can greatly impact the beam spray which will impact the dose range
- Consider where metal might stack on metal or heavy plastic handles should be alternated

Contract Manufacturer Changes

- Minor changes to processing that you're unaware of can greatly impact bioburden and fail a dose audit

PULSE ON REGULATORY

Sterilizer Equipment Validations

- FDA has requested equipment installation, operational and performance qualification reports
- Not easy to get from some service providers – plan accordingly

Laboratory Testing for Bacteriostasis / Fungistasis (aka Sterility TMV)

- FDA wants all 5 standard organisms
- Regardless of the sterilization method, and what the ISO standards recommend

"Representative Samples" – Justification needs to be in protocols

- Clients have had to repeat testing due to samples tested being prior generation, not fully processed, processed in different environment or not similar material concentrations

STANDARDS

ETO	RADIATION	STEAM	LIQUID CHEMICAL	HYDROGEN PEROXIDE
ISO 11135-1:2014	ISO 11137-1:2006	ISO 17665-1:2006	ISO 14160:2020	ISO 22441:2002

SUMMARY

Sterilization can greatly impact the success of a project. From budgeting to timelines to acceptance by regulatory bodies, it's not the smallest piece of the puzzle….

THANK YOU

Darci Diage Ward
darci@tplconsulting.net