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Introduction to Ethylene Oxide Sterilization and Regulatory Updates

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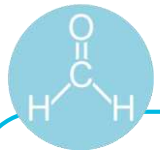
Agenda

- Regulatory overview
- Ethylene Oxide Sterilization
- Process Definition
- Performance Qualification

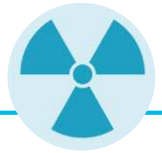
Regulatory overview

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

History - ISO 11135

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)

ISO/TS11135-2:2008 – Sterilization of health care products – Ethylene Oxide
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
- *European Pharmacopeia* (EP) Chapter 2.6.14 Bacterial Endotoxins
- *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

1859 — **Ethylene Oxide discovered**
Charles Wurz

1925 — **First production of Ethylene Oxide**
Union Carbide Chemicals

1938 — **Patent for sterilization of spices**
Lloyd Hall

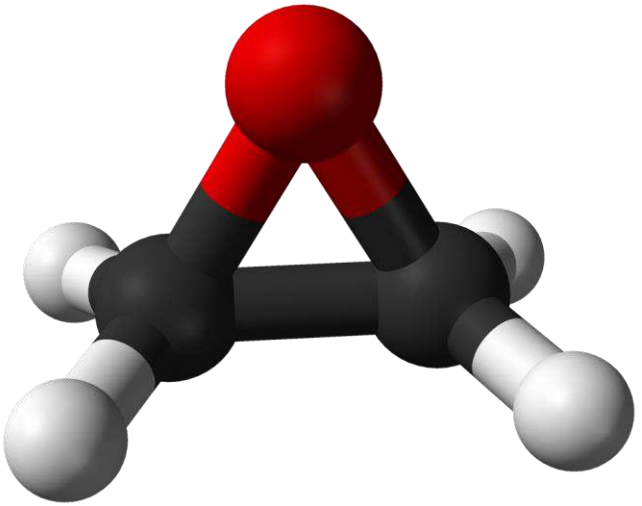
1940 — **Use in sterilization of materials**

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

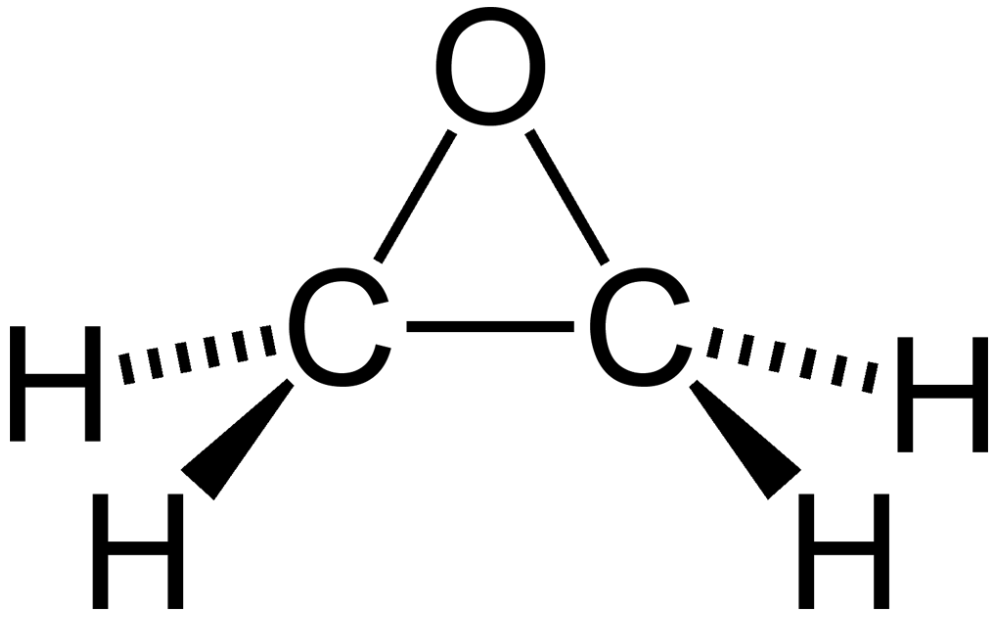
- Toxic gas
- “Sweet smell” from ca. 500 ppm concentration
- Forms with air explosive mixtures (2.6 %)
- Oncogenic by inhalation
- Irritating for skin and respiratory system
- Mutagenic for animals and very likely for humans



Ethylene Oxide

Mode of Action

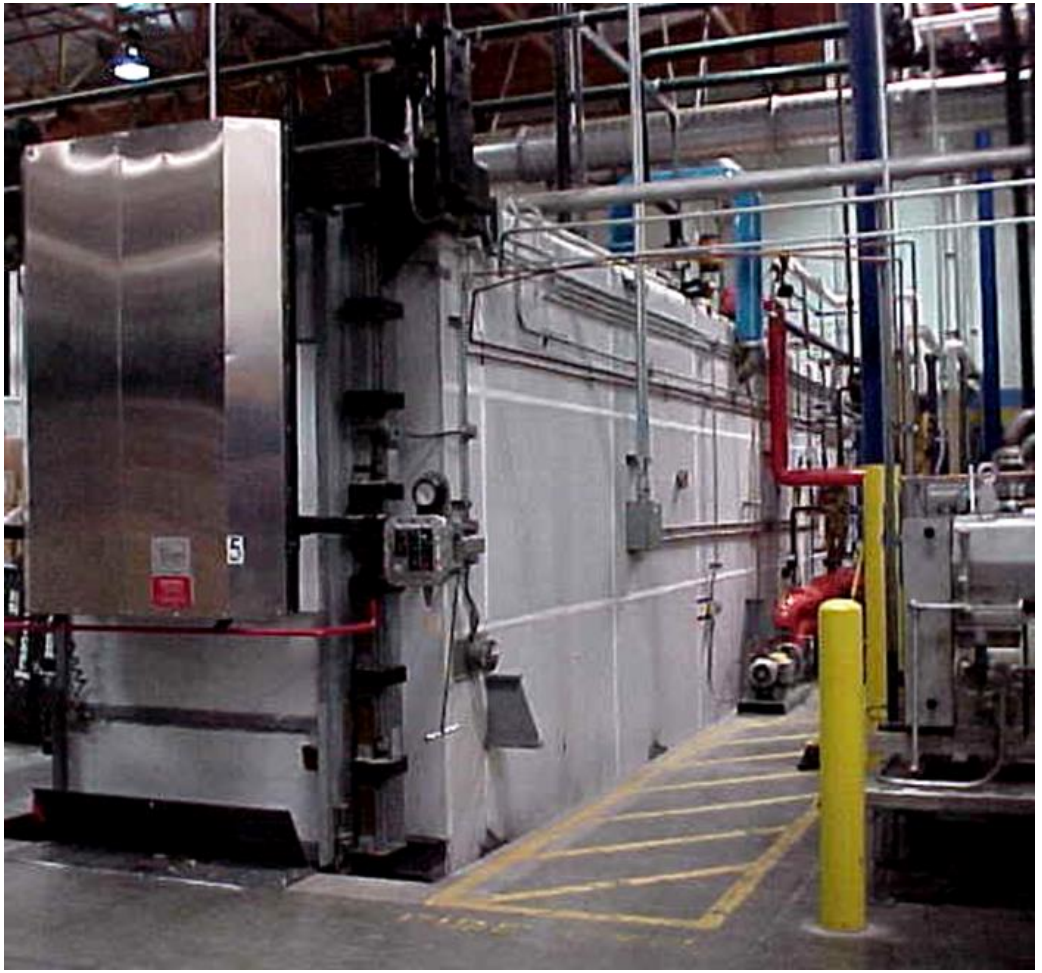
- Extremely reactive
- Irreversible reaction with DNA and proteins (alkylation)
  - The molecule is loses function
  - Replication stops
  - The cell dies



Ethylene Oxide Sterilization

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

- Heat-sensitive material
  - Products that cannot tolerate the high temperatures of Moist Heat (Steam) Sterilization
- Material sensitive to ionizing radiation
  - Products can embrittle and discolor over time after exposure to ɣ, E-beam, X-ray

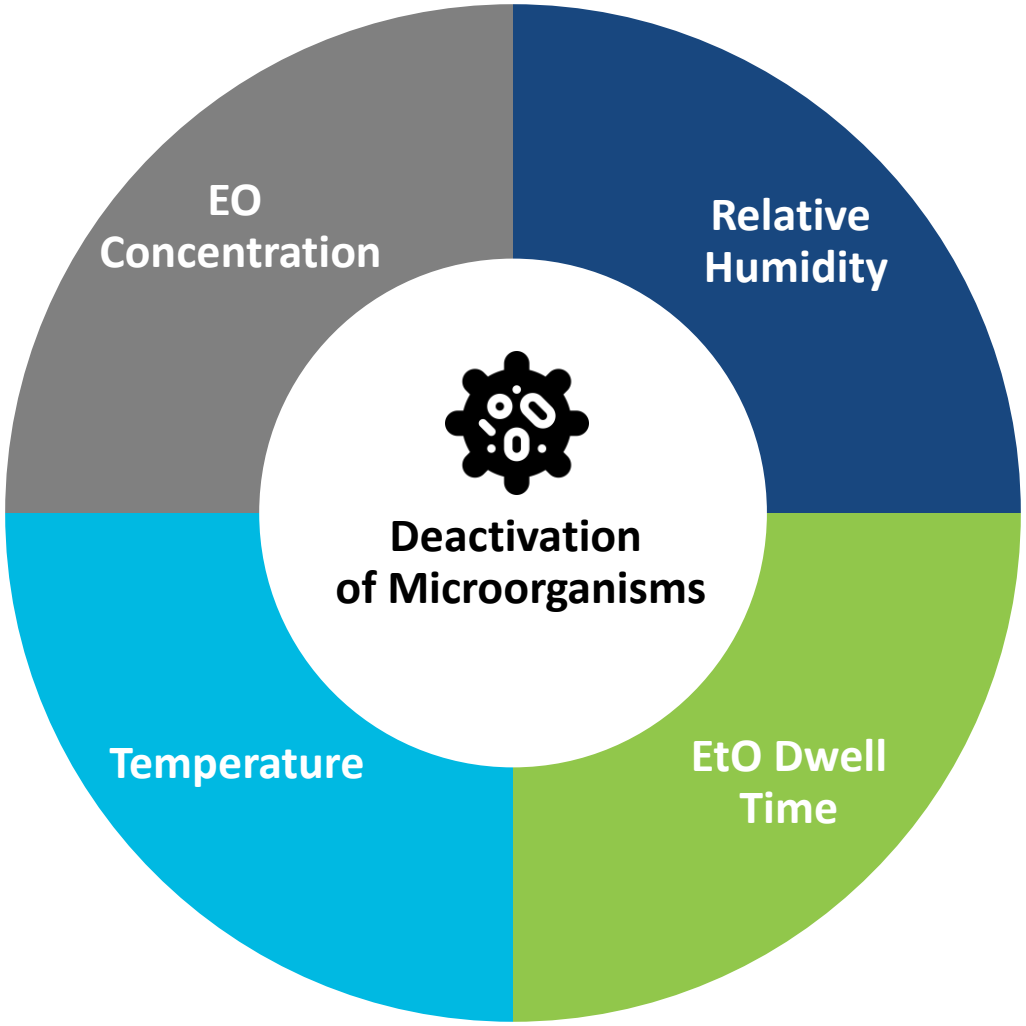


Considerations When Sterilizing Using Ethylene Oxide

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



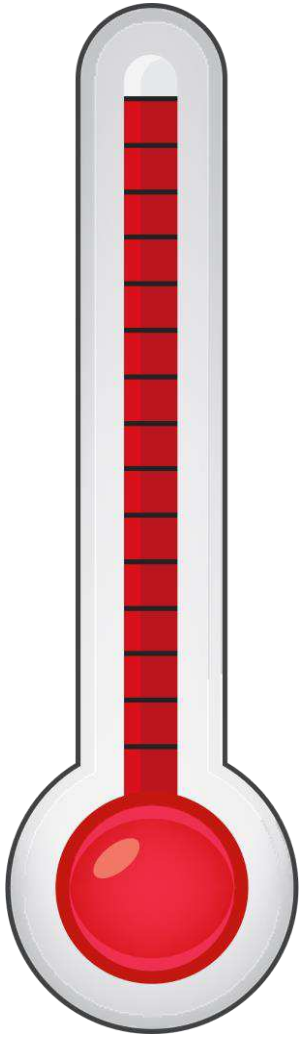
Temperature (T)

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

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

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

Temperature increase may increase of permeability of gases through materials

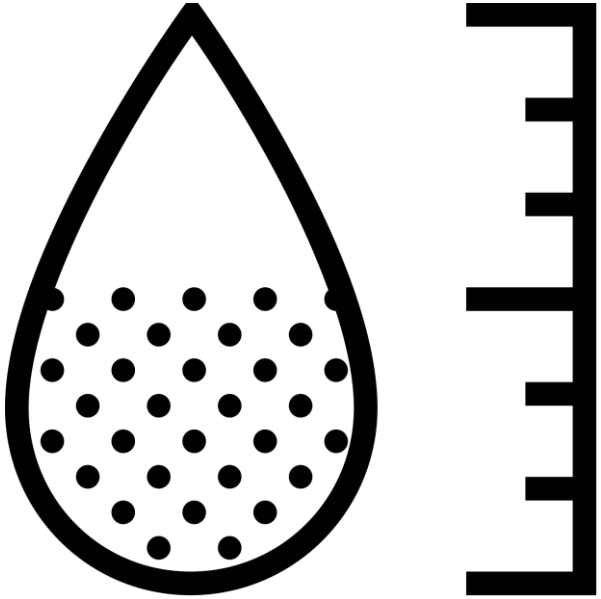


Relative Humidity (RH)

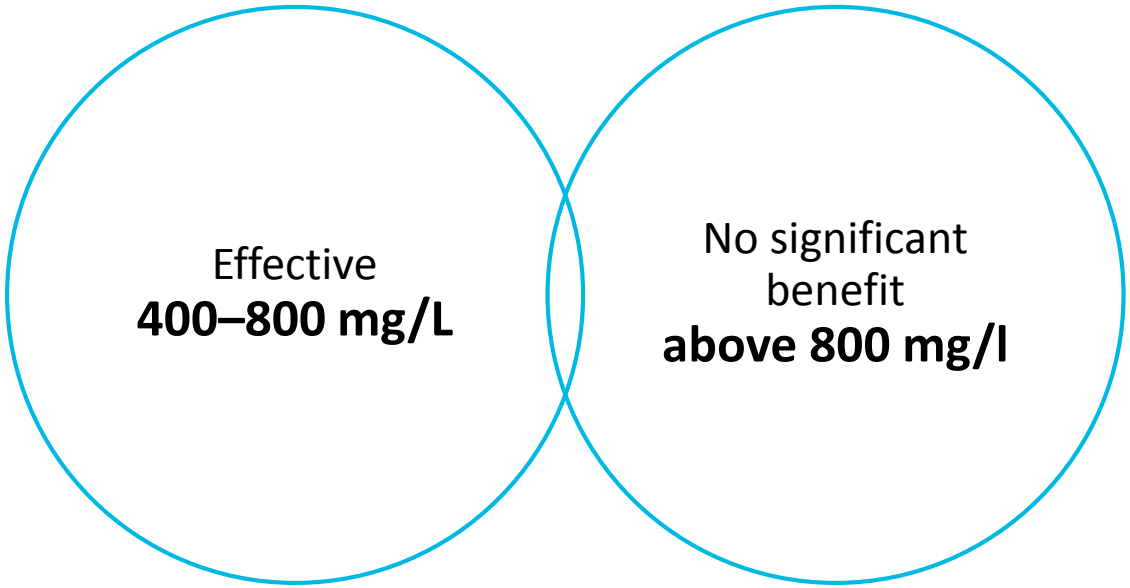
Necessary for **alkylation reaction**

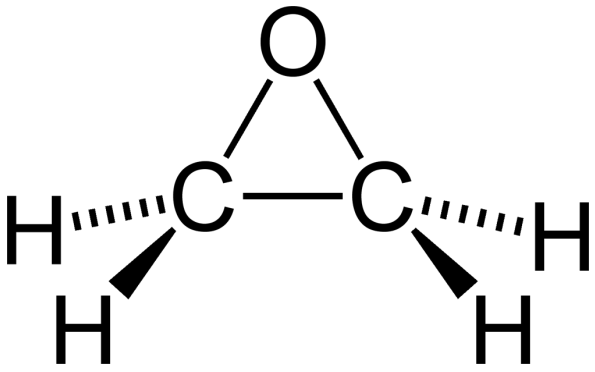
Relative humidity may assist penetration of EO through materials

EO is most effective at **RH > 30%**



EO-Concentration





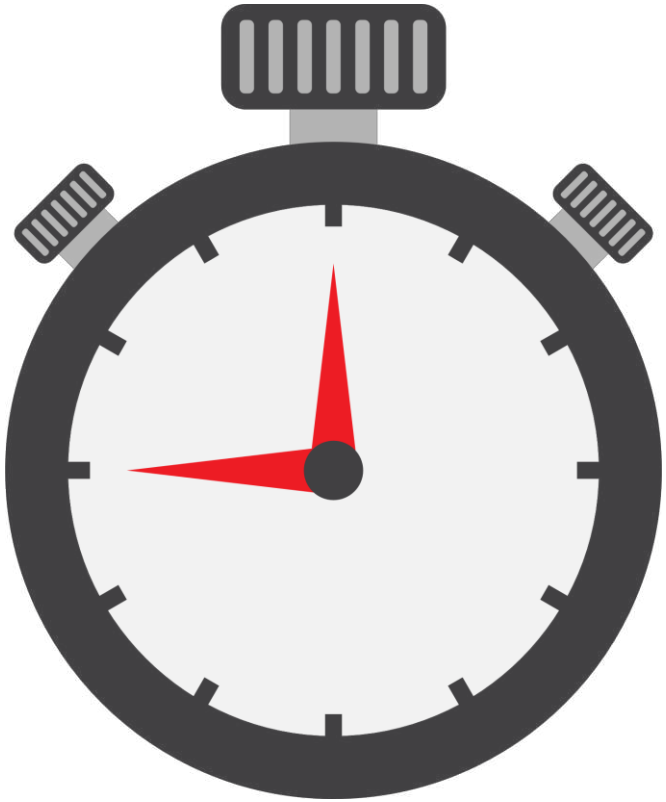
At constant T and RH – if EO concentration increases microbiological Deactivation is more effective - up to c. 800 mg/l

- ~ 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



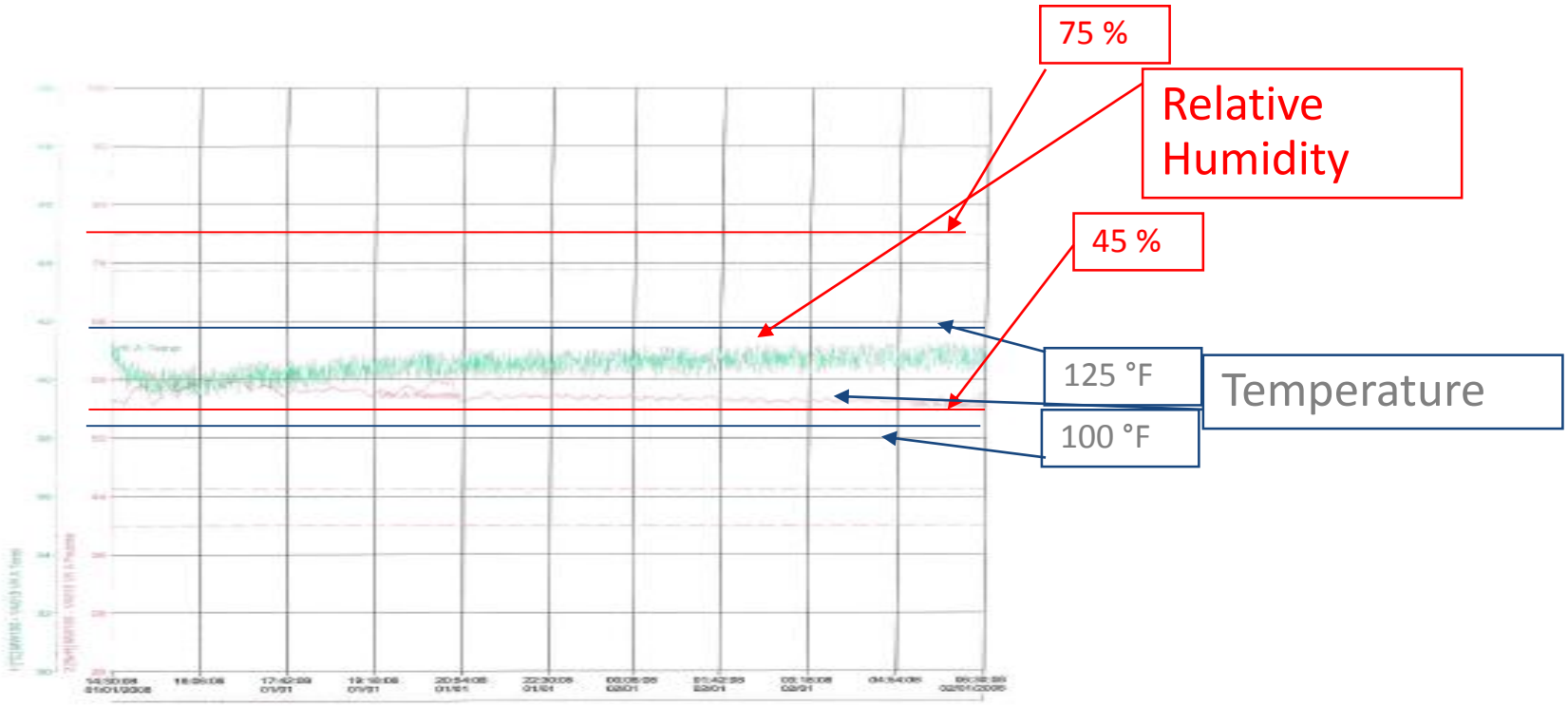
Sterilization Process

The sterilization process has 3 key phases

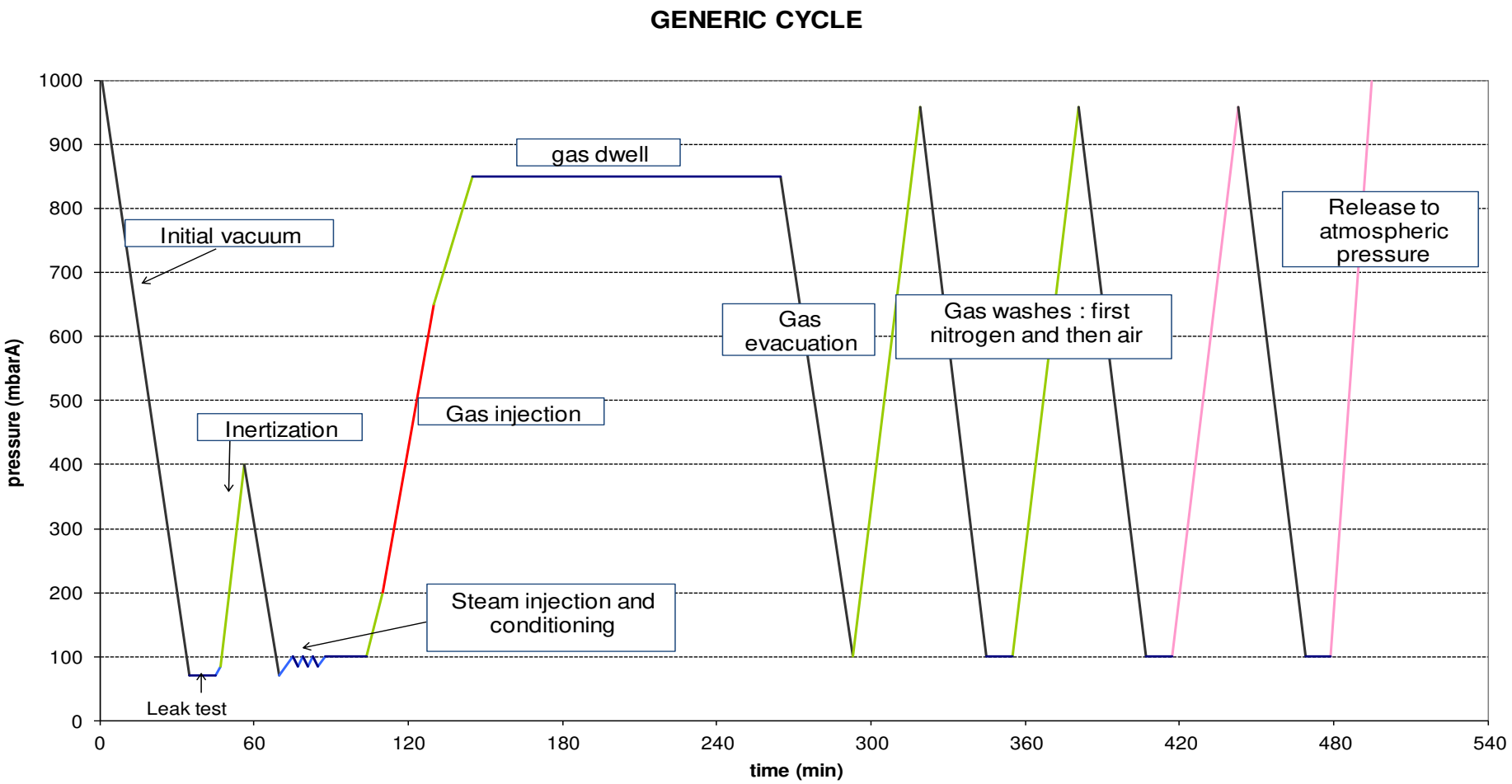
Preconditioning

Preconditioning, typically:

- 35–45 °C
- 45–75 %RH

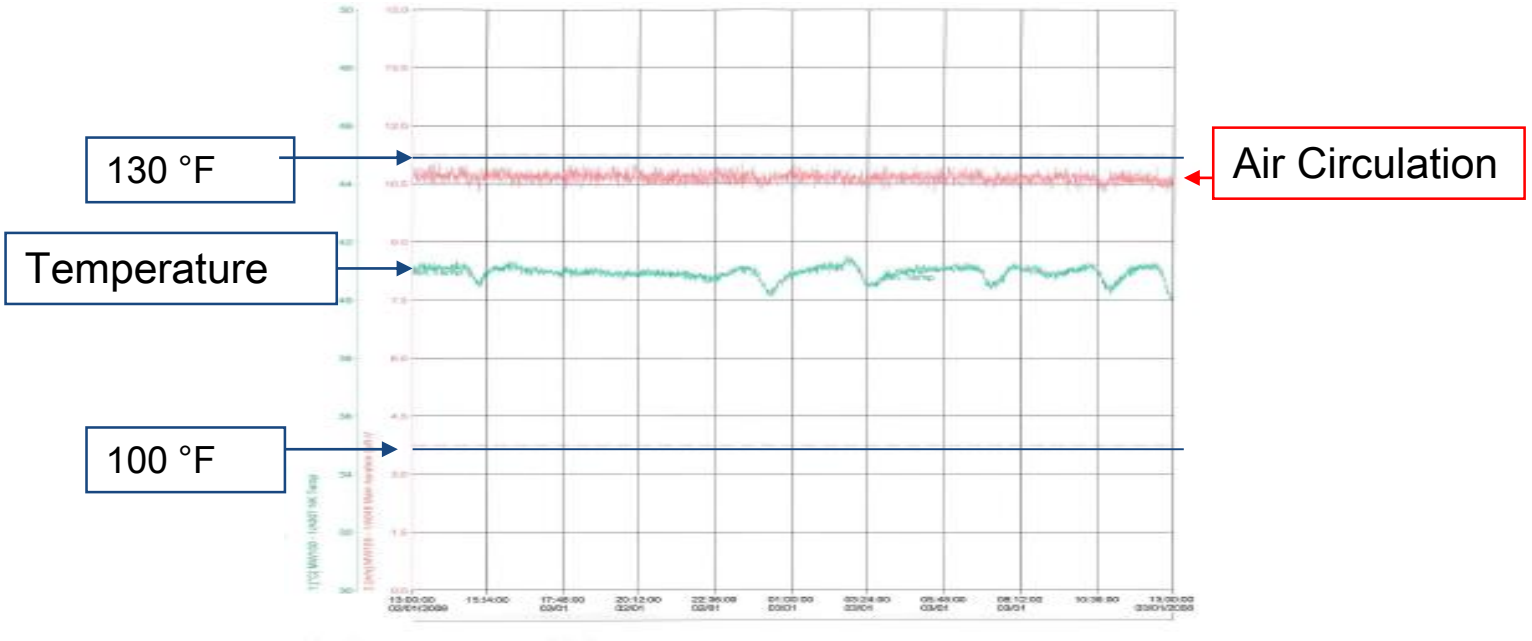


Typical EO Cycle Design – Deep Vacuum



Aeration

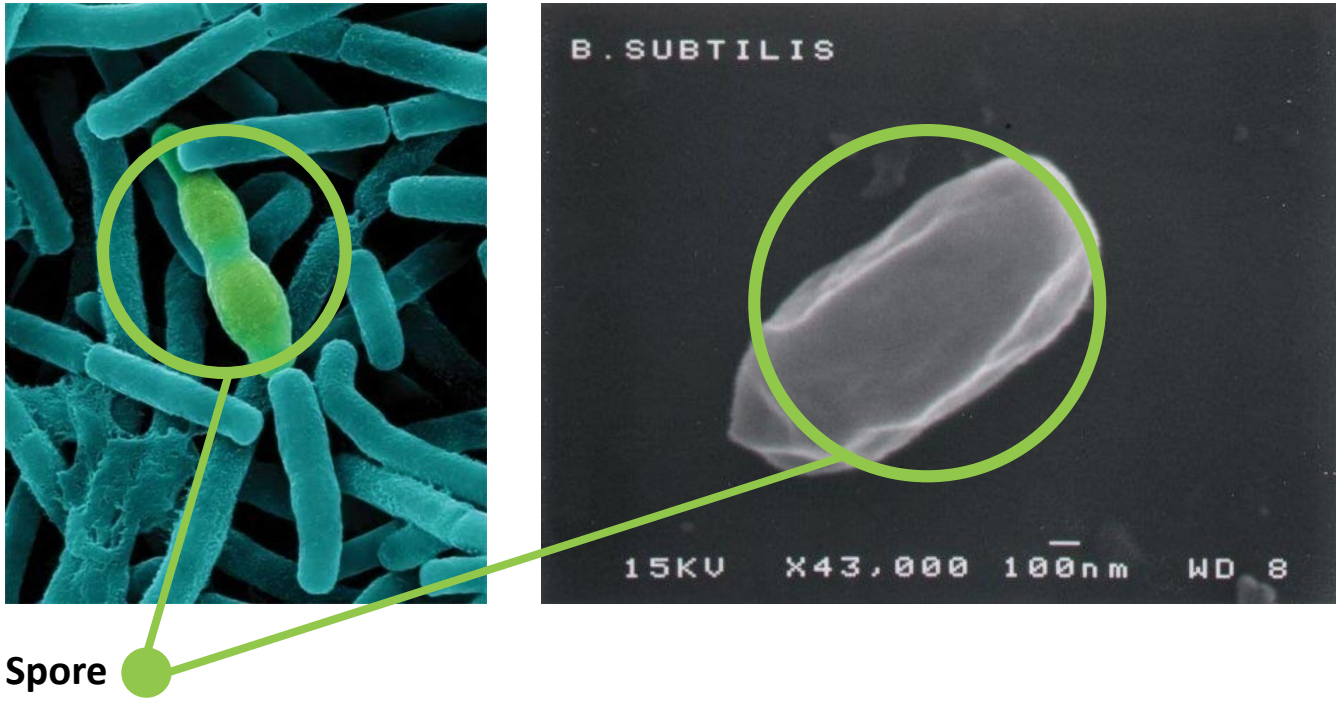
- Aeration, typically:
  - 35 – 50 °C
  - Forced circulation



Monitoring EO Sterilization Processes

Monitoring EO Sterilization - Biological Indicators

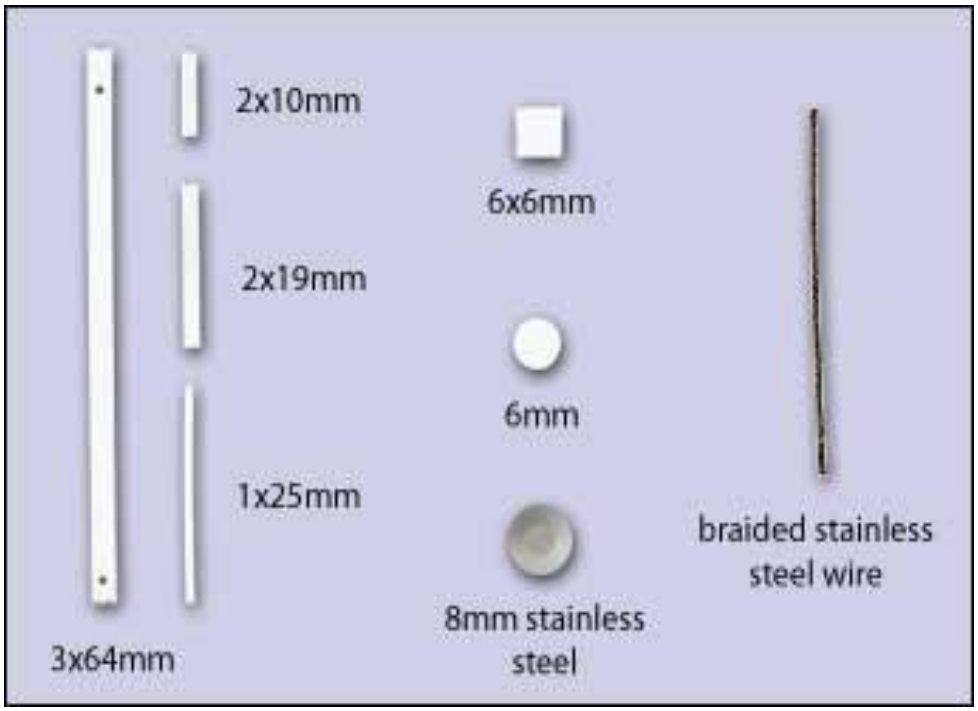
- Usually, the BI contains at least a million spores of an organism that is highly-resistant to the EO process.
- The name of the bacterium is commonly *Bacillus subtilis* or *B. subtilis*.
  - It has been renamed and is officially *B. atrophaeus*.

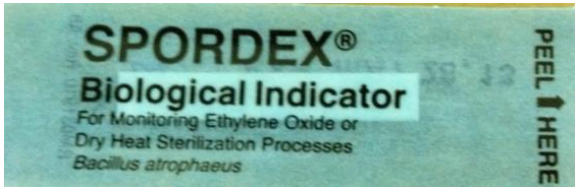


Monitoring EO Sterilization - Biological Indicators

Biological Indicators (BI)

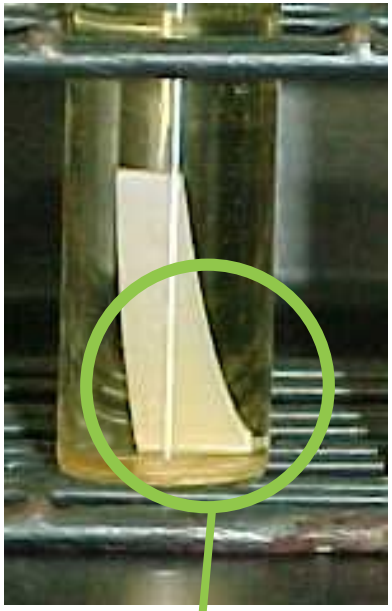
- >10^6 Spores of resistant strain *Bacillus atrophaeus*
- Can come in many different designs



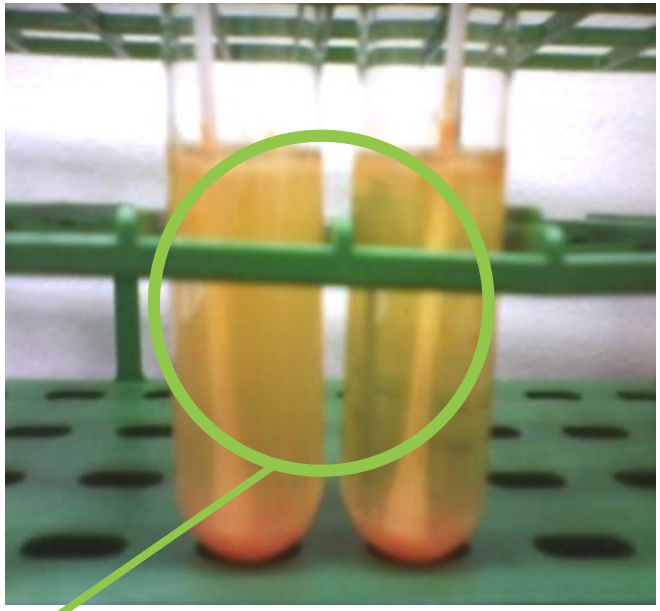


Monitoring EO Sterilization - Biological Indicators

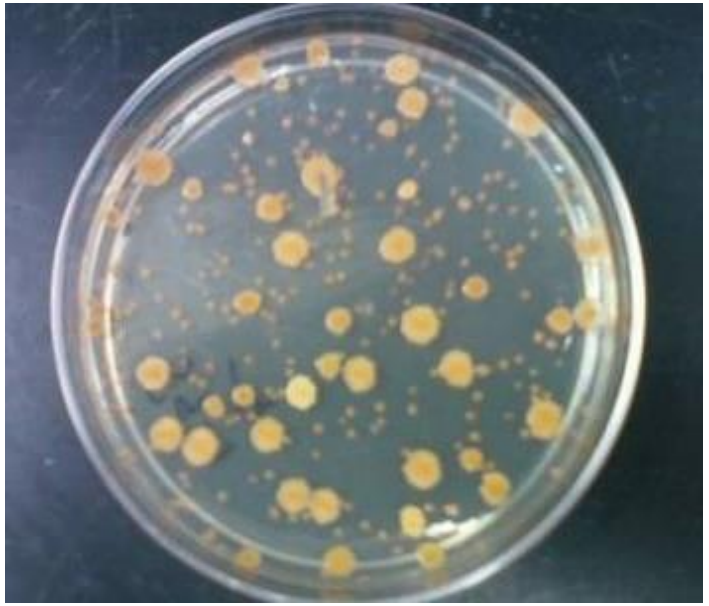
Negative: No Growth



Positive: Growth



Morphology

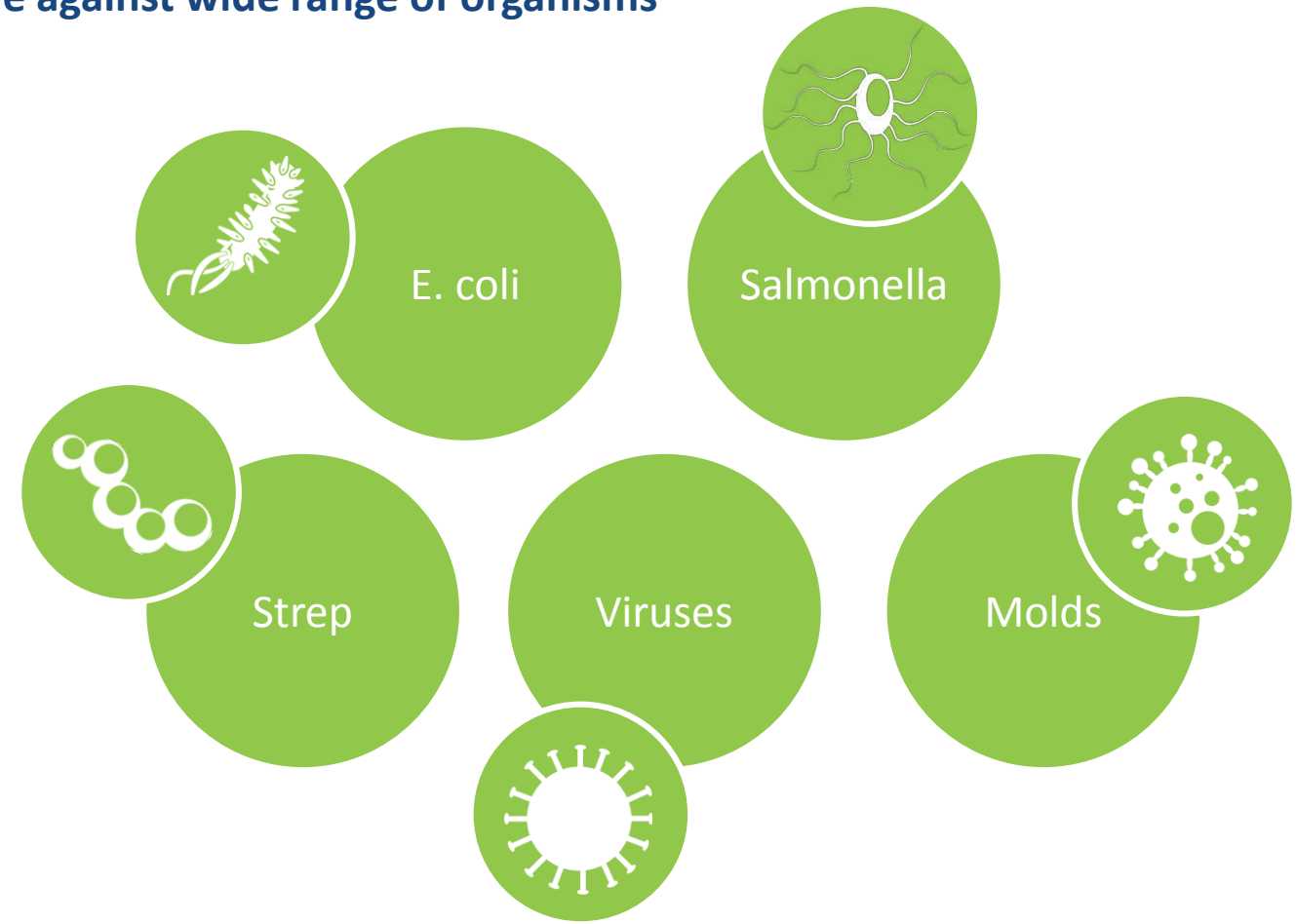


BIs in vial with Medium

Monitoring EO Sterilization – Biological Indicators

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



Process Definition

ANSI/AAMI/ISO 11135:2014

- 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

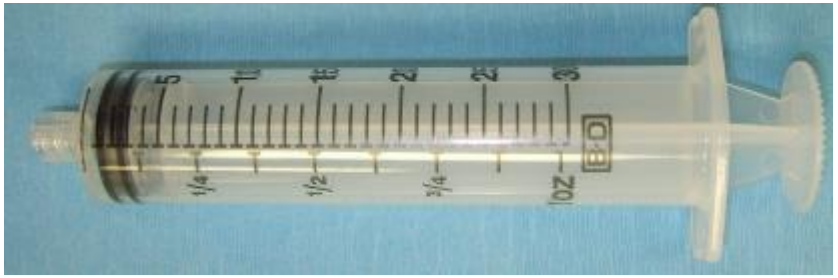
Load Configuration

Bioburden

Internal PCD

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

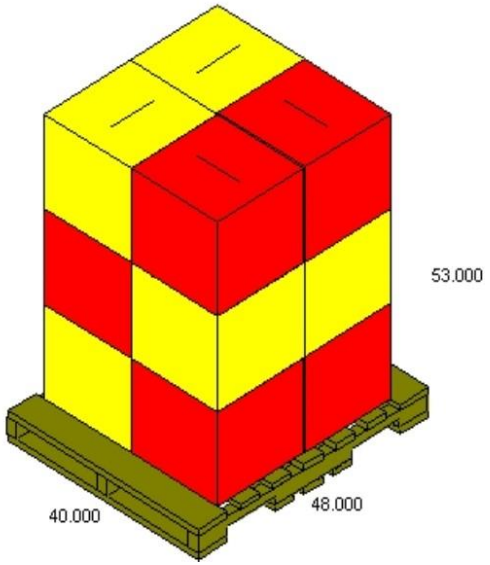


Product Families

- 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)

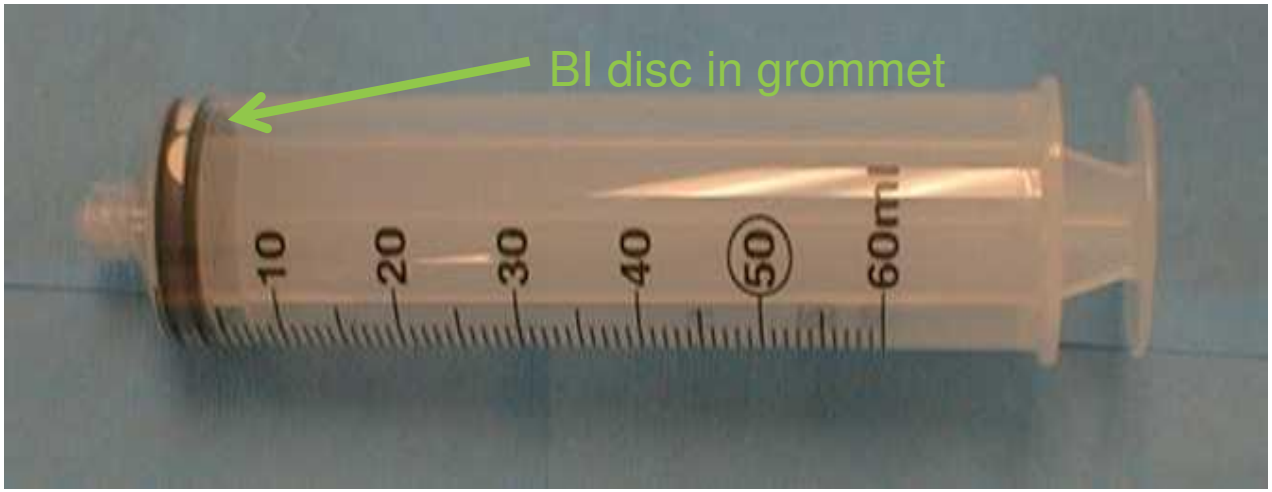


Process Challenge Device (PCD)

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)

Internal PCD



External Process Challenge Devices

Also known as:

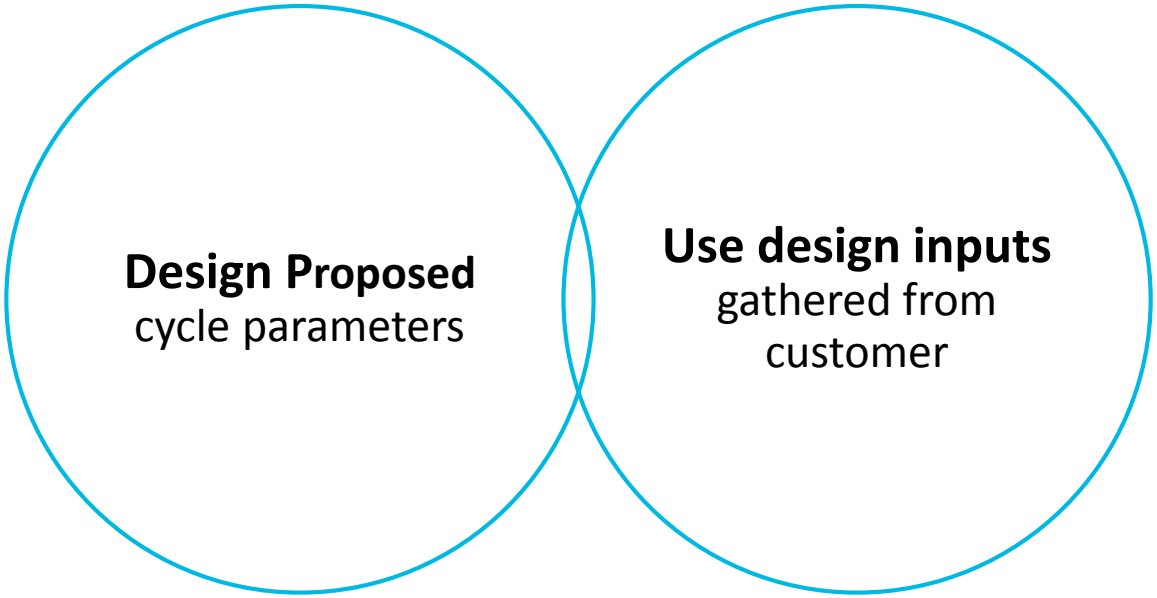
EPCDs

Test Packs

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

External PCD

Next Steps


Design Proposed
cycle parameters
Use design inputs
gathered from
customer

Fractional Runs

ANSI/AAMI/ISO 11135:2014, section 8.6

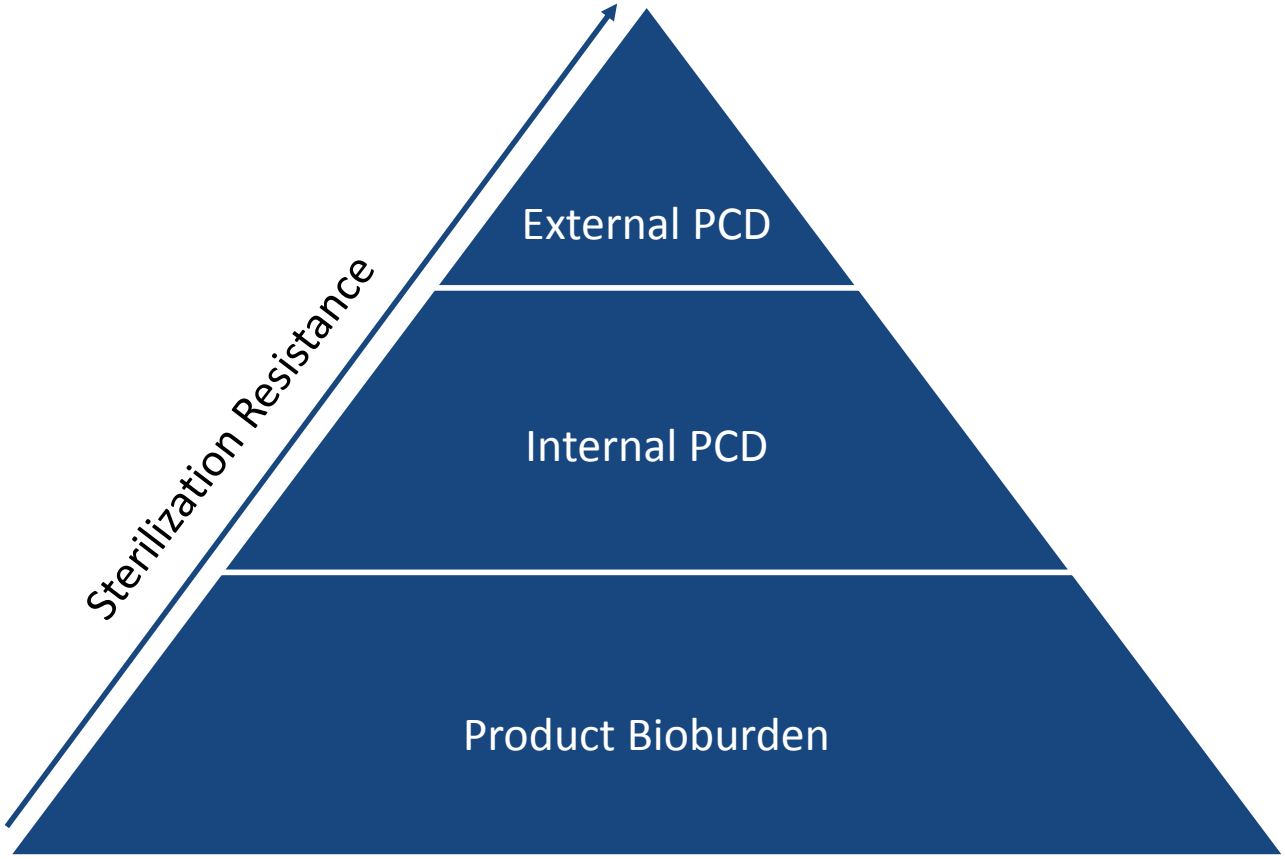
Also known as ‘sublethal’

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

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]

Hierarchy required



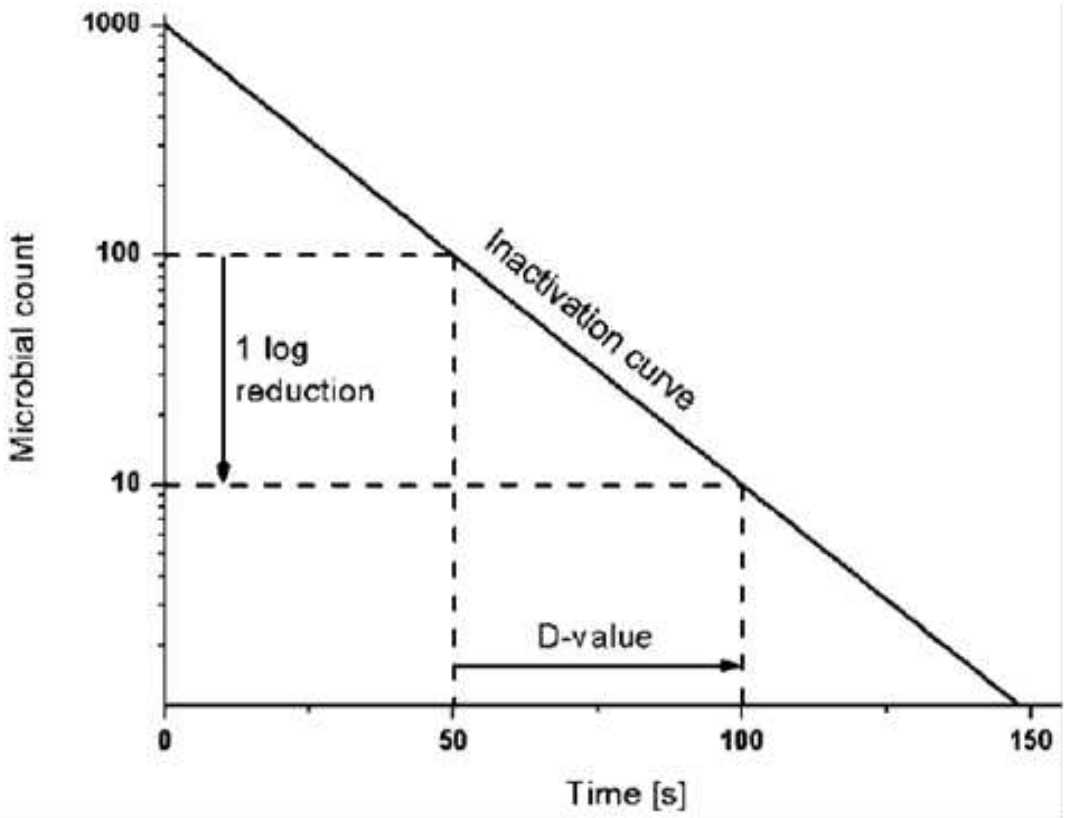
Define Half Cycle Gas Dwell Time

- 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)

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

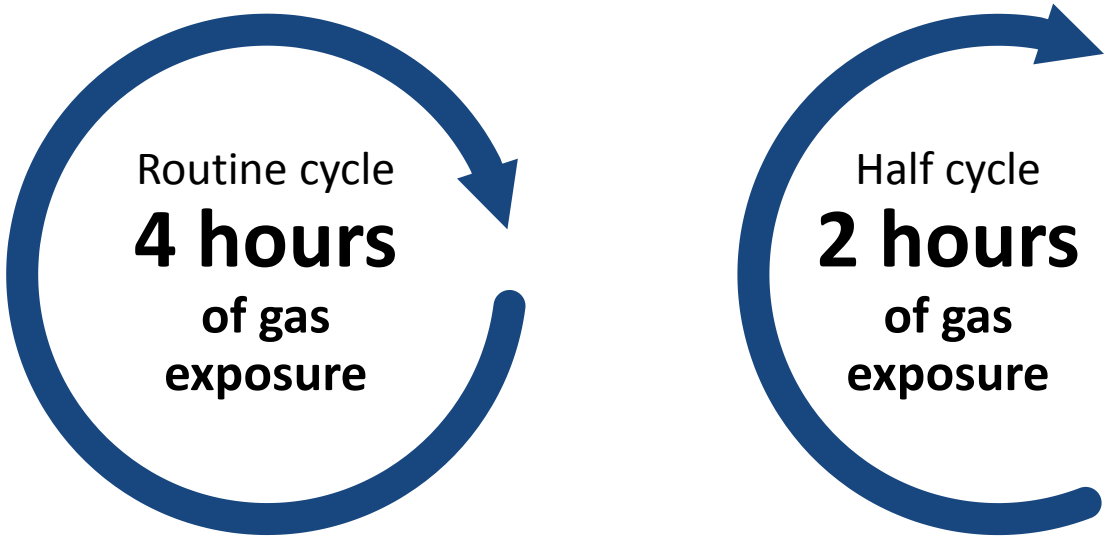
Performance Qualification

ISO 11135:2014

- PQ consists of both microbiological and physical performance qualification and is performed in the equipment used to sterilize the product
  - Microbiological Performance Qualification (MPQ) and
  - Physical Performance Qualification (PPQ)
- Operationally these are referred to as the half and the full cycles, respectively

What is a “Half Cycle?”

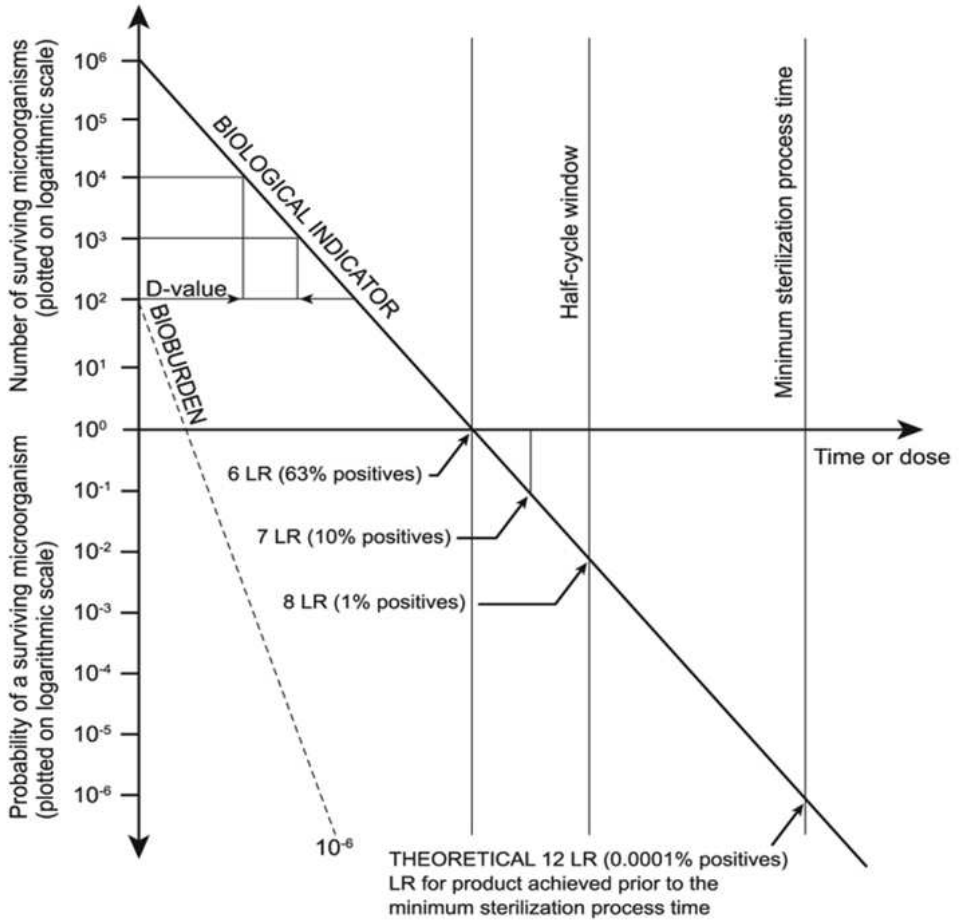
Compared to the normal type of cycle that you will run in routine production, the “Half cycle” uses one-half of the EO gas exposure time



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.



AAMI TIR 16: 2009 section 5.1.1

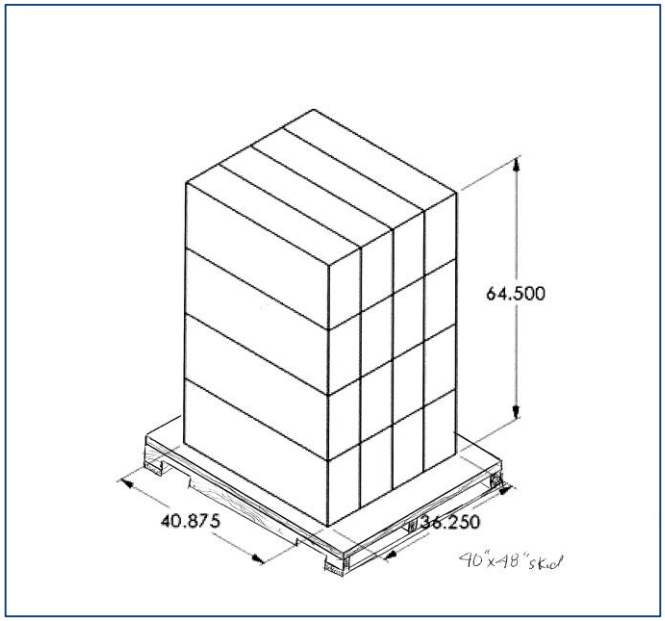
"A typical performance qualification requires three consecutive successful validation cycles to demonstrate reproducibility the first time the cycle is validated. The first successful cycle indicates that the proposed cycle lethality is **achievable**. The second successful cycle indicates that the cycle 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)
  - Temperature
  - Humidity
  - Pressure / Gas Concentration
  - 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

Full Cycles

- 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 Steriliy Assurance Level

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