SVC

Reducing EtO use in sterilization cycles by changing sterilization load configuration

Dennis Christensen

1836 Stone Avenue

San Jose, CA 95125

Cycle Validation

The first step is the most important step;

*"Where is **the most difficult place to sterilize** in your product?"*

ISO 11135:2014 requirement:

B.2.1 Create a challenge to the sterilization process, Process Challenge Device (**PCD**), comprising a known number of microorganisms with known resistance to ethylene oxide (**EtO**), by placing biological indicators (**BI**) in the product or inoculating product at locations where sterilizing conditions are most difficult to achieve. If the location(s) of the microbiological challenge is other than the most difficult-to-sterilize within the product, its relationship to the most difficult location(s) shall be established.

Cycle Validation

Challenge is knowing where the most difficult BI location to sterilize is within a product:

Example**: Syringe**

1. Inside the stopper below the plunger?

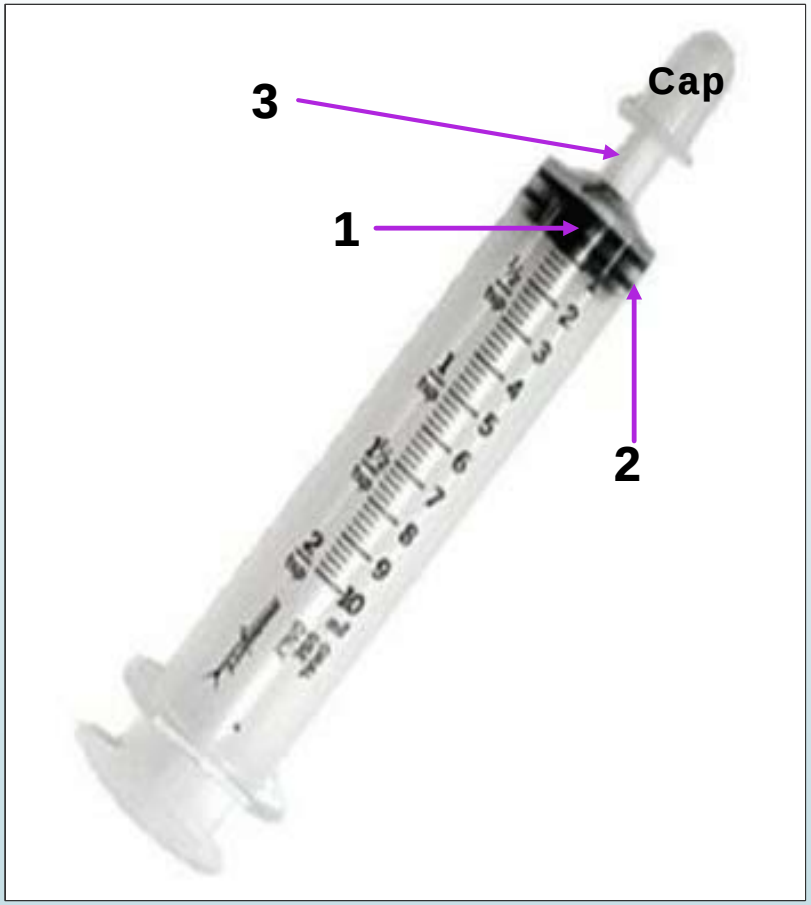
- Plunger design and fit into the stopper well?

2. Around the ribs of the stopper?

- Material of stopper?
- Dimensional tolerances?

3. Below the stopper with luer cap attached?

- Vented or non-vented cap?



Cycle Validation

Most Important Cycles in any Validation is the Fractional Runs;

- Documents the ability to sterilize the natural product bioburden and documents that the Internal Process Challenge Device (**IPCD**) is more difficult to sterilize.
- Test data documents the most difficult to sterilize location of BI in product – IPCD has to have some survivors.
- Cycle can be used to document the comparative resistance of the IPCD to a Master Challenge Product (**MCP**)
- Data establishes the MCP is equal or preferably more difficult to sterilize than the IPCD.
- Data must document an EPCD that is equal or more difficult to EtO sterilize than the IPCD and/or the MCP.

Packaging

Each layer of packaging increases the time required for relative humidity (RH), temperature, and EtO to penetrate into the product.

Product packaging –

- Single or double pouches with Tyvek
- Petg tray with Tyvek lid
- Pouch with strip of breathable Tyvek.

Packaging

Shelf Carton

- Placement of breathable side of product packaging within the shelf carton.
- Placement of instruction for use (IFU) on breathable surface.

Example:

Packaging

Palletizing for Sterilization

- Cardboard Box – weight of corrugated?
- Pallet Configuration? Change for ease of access and removal of RH and EtO
- Stretch Wrap – Thickness? Number of layers?
- Open or closed stretch wrap?

ISO11135 Annex A - Overkill Validation

Most common method of validation for EtO

Is minimum of one fractional and three ½ (half) cycles:

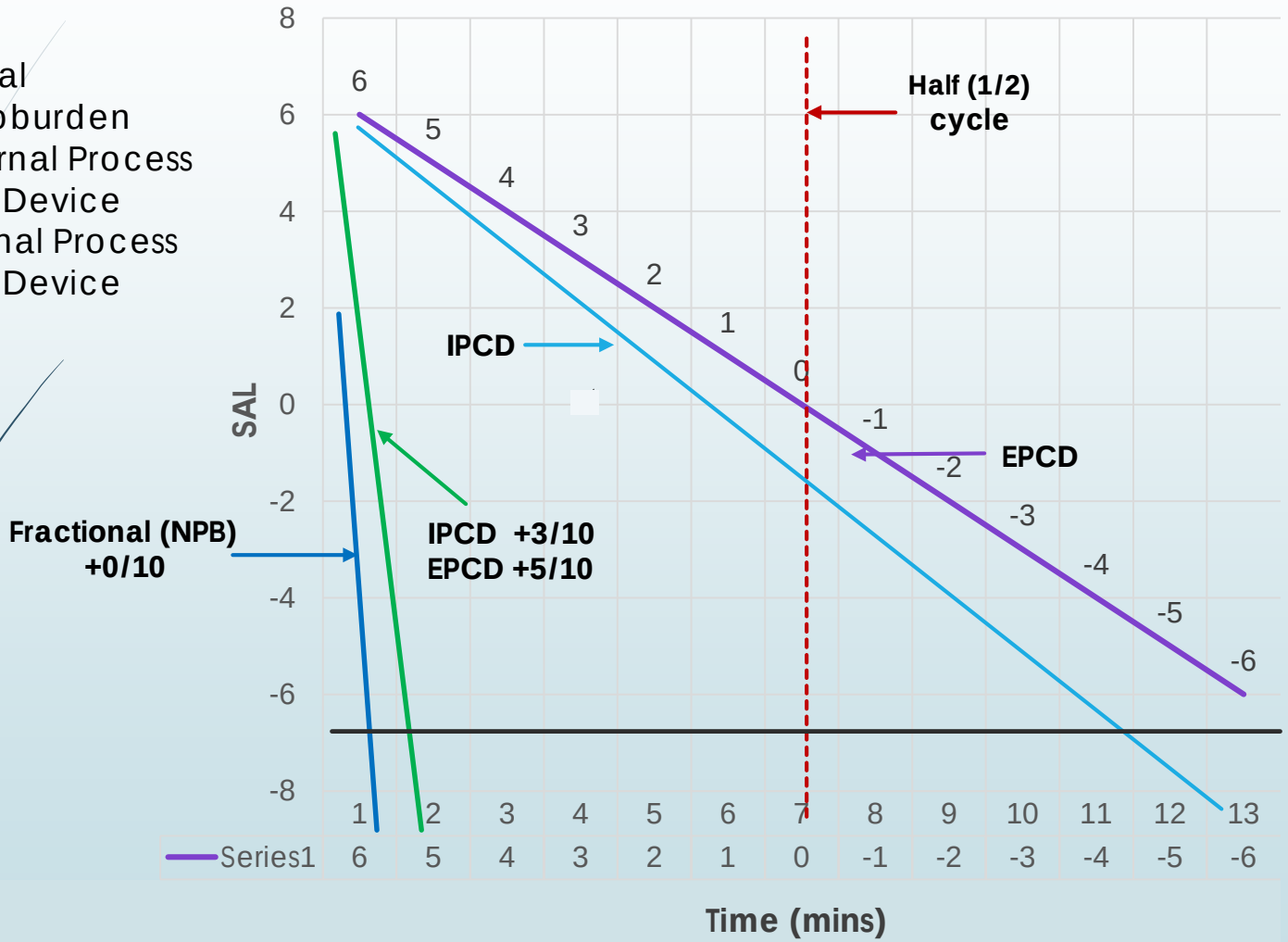
- Fractional cycle(s) are very short EtO exposure.
- Half cycle EtO exposure time is estimated; typically at a longer than required time to achieve good test results.
- Full cycle is double the EtO exposure time of the ½(half) cycle; therefore, much longer exposure time is used than is probably required for full cycle.

Minimum of 10^{-6} Sterility Assurance Level (SAL) but **actual SAL could be much greater**.

SVC- Current Overkill Validation

SAL 10^{-6} (Sterility Assurance Level)

NPB=Natural Product Bioburden
EPCD=External Process Challenge Device
IPCD=Internal Process Challenge Device



Example of Cycle Development

- A company spent $90,000 and 8 months trying to develop an EtO sterilization cycle.
- A contractor was up to an [redacted] EtO exposure time and still had positive BI's inside the product.
- The product exposures were within a box *with closed* cell foam…….

Example of Cycle Development

- This company then contacted SVC for consultation on a new cycle development.
  - SVC eliminated the cardboard box and the closed cell foam for the new cycle development.
  - SVC used same internal product and same BI location in product.

Results: SVC had 100% BI kill at [redacted] using same EtO concentration, temperature, and RH.

Plan: to validate a much shorter EtO cycle for the same product without using the closed cell foam and corrugated box.

Actual Data for this product Cycle Development

	Contractor with Box/Foam	SVC W/O Box/Foam
Temperature	45°C	45°C
Relative Humidity	60%	60%
EO Concentration	600 mg/liter	600 mg/liter
EO Exposure Time	>16 Hours	< 3 Hours

ISO11135 Annex B - BI/Bioburden Validation

Uses multiple fractional cycles to:

- establish BI resistance with positive BI's, and
- calculation of the cycle lethality.

Cycle development can use reduced EtO concentration for fractional runs.

Major Benefits:

- Full cycle EtO exposure times will generally be much shorter than Overkill method (exposure time)
- Product EtO residuals should be less due to lower EtO concentration and shorter EtO exposure times

BI/Bioburden Validation Method

SAL 10^{-6} (Sterility Assurance Level)

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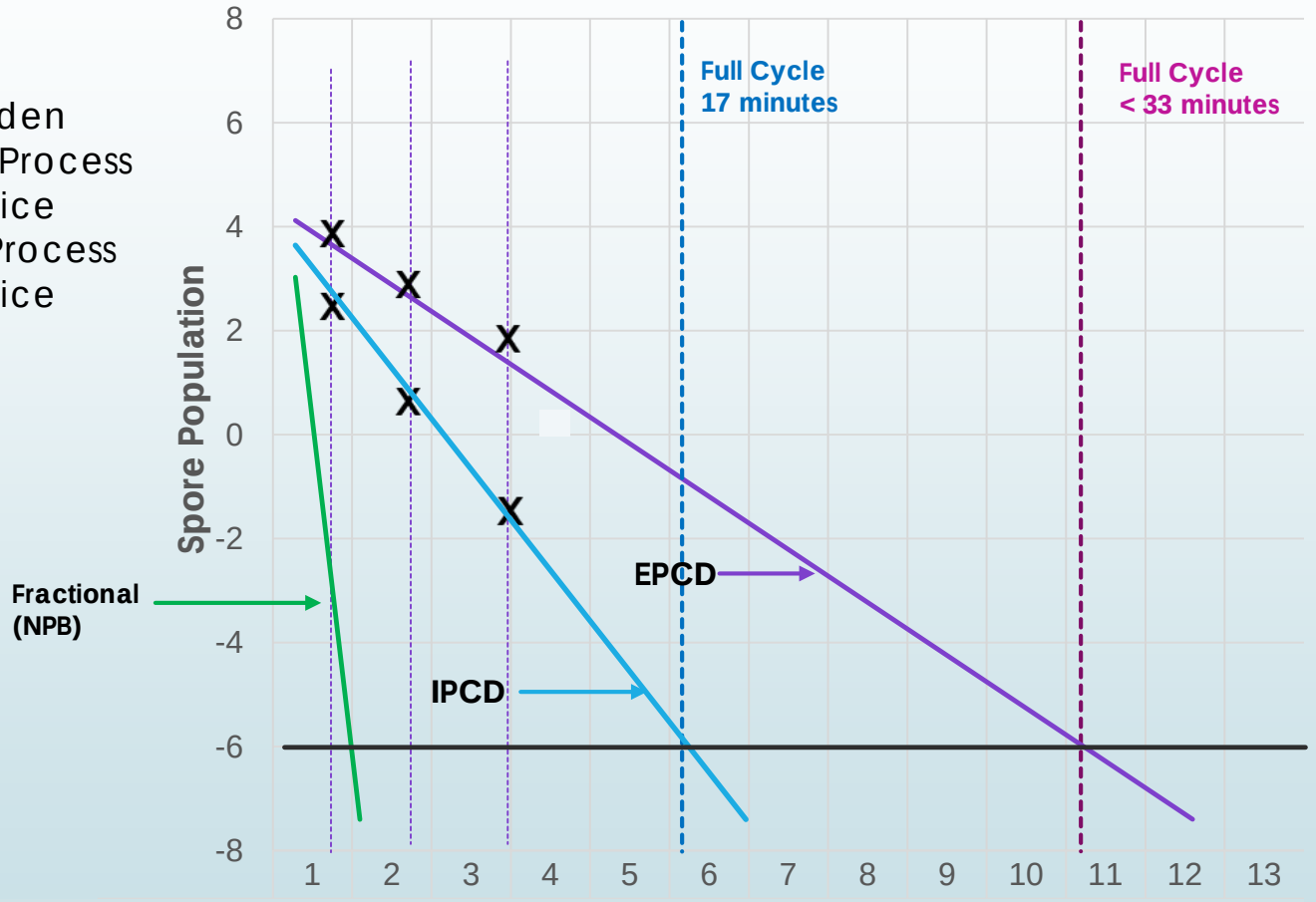

Benefits of BI/Bioburden

- Use less EtO per cycle – **significant cost saving $$$**
- Shorter EtO exposure time thus more EtO capacity
- Less aeration time expected
- Expected lower product EtO residuals
- Potentially lower EtO employee exposure

Concerns:

- Need to develop EPCD that works at significantly lower EtO exposure time then Overkill
- Auditors understanding the BI/Bioburden "concept"

Estimated Benefit to SVC

SVC in 2020 will run approximately 2000 cycles

If BI/Bioburden Validation is successful:

- the weight of EtO used for processing would be reduced from 750 pounds to ≤ 500 pounds or ~35% reduction,
- the available sterilizer capacity will increase ~25% as a result of shorter Eto cycles, and
- the discharge from the Abator will be reduced.*

*SVC limit for the facility annual EtO discharge is less than 0.95 # per year for all six sterilizers

Change Control
ISO11135 & AAMI TIR 28

- Changes can be to modified products, add brand new products or company makes packaging changes.
- Section D.7 of 11135:2014 and Technical Information Report (TIR) 28 provides guidance on how to evaluate product package changes.
- Important to document any changes to establish rational for what additional testing, *if any*, is required to maintain validation.

Change Control
ISO11135 & AAMI TIR 28

Possible actions for validated product are:

- Letter to file to document review
- Additional ½ or fractional cycle
- Full new validation
- Repeat EtO residual work
  - New EtO dissipation curve
  - Single point to document no change

Something to Consider

- Sterilization is measured in D values
  - One D value is the time required for the sterilization process to reduce the spore population by one log (e.g. 10^6 to 10^5)
- Almost all medical devices have a natural product bioburden of <500 colony forming units (CFU)
- Natural product bioburden is distributed across the entire product surfaces and the bacteria is generally less resistant than the spore carrier used in validation
- ***11135-Overkill*** method requires a **minimum** of 1,000,000 spores for BIs
  - For validation BIs must be placed in the most difficult location to sterilize in product
- Consideration *should be* given to lowering the minimum required spore population in the most difficult location to sterilize to >1,000
  - Going from 10^6 to 10^3 would reduce the required full cycle Eto Exposure time by an estimated **25%**

Something to Consider

- Sterilization is measured in D values
  - One D value is the time required for the sterilization process to reduce the spore population by one log (e.g. 10^6 to 10^5)
- The D value of Bis used for EtO sterilization have an average D value of 3 – 5 minutes.
- The D value of biological indicators used in alternative gas sterilization validation have an average D value of ≤ 1 minute.
- *Can a lower D value biological indicator be developed for EtO sterilization?*

Benefit: **Reduced EtO exposure time for all EtO cycles.**

That's all folks!