TECHNICAL TIP

PERFORMANCE QUALIFICATION OF AN ETHYLENE OXIDE STERILIZATION PROCESS METHOD C

Overview and detailed steps of Process Method C

There are several different methods for performance qualification of an ethylene oxide process for sterilization of a medical device or component. The most common, and the subject of this Technical Tip, is the Method C (or overkill method) as listed in the guidelines published by the Association for the Advancement of Medical Instrumentation (AAMI). This is the most common and cost-effective method utilized in the industry today.

ANSI/AAMI/ISO 11135[1] (note the reference to the International Standards Organization) describes the qualification process for a Method C as follows:

"This method involves determination of the minimum time of exposure to ethylene oxide, **with all other process parameters held constant**, at which there are no survivors (biological indicators). Two further experiments should be performed to confirm the minimum time. Both should show no growth from the biological indicators. The specified exposure time (routine) should be at least double this minimum time. A cycle of short duration from which survivors can be recovered should also be run to demonstrate the adequacy of the recovery technique."

The qualification method described above is very similar to the method described in the old guidelines published by AAMI, titled "Guidelines for Industrial Ethylene Oxide Sterilization of Medical Devices."[2] As in the new guidelines (11135), three half cycles (one half of the routine gas exposure time) were conducted in which a 10^6 biological indicator is reduced to 0 spores when it is placed in the most difficult to sterilize location within the medical device and within the sterilizer load.

NOTE: Biological indicators used to monitor the ethylene oxide sterilization process typically consist of a greater than 10^6 (1 million) population ofBacillus atrophaeus typically inoculated on a paper carrier. This is the indicator of choice as identified in the U.S. Pharmacopeia[3] (USP31).

The difference in the new AAMI guidelines as compared to the old guidelines is the addition of a "cycle of short duration" (termed "fractional") which produces biological indicator growth, thus validates the biological recovery process. Also as an added benefit, the fractional cycle may be utilized to establish a relationship between a biological indicator placed on the outside surface (external) of a pallet and the biological indicator placed in the most difficult to sterilize location (internal). This data may allow routine monitoring using only external biological indicators, thus preventing internal biological indicator monitoring. This is a great advantage since the cartons do not have to be opened, which prevents potential operator exposure to elevated levels of ethylene oxide.

Monitoring of internal load temperatures and relative humidity is also a requirement of performing qualification processes which comply with the guidelines established in ANSI/AAMI/ISO 11135. Compliance to British Standard EN550[4] may be achieved by adding additional monitoring sensors beyond those referenced in ANSI/AAMI/ISO 11135. The total number of sensors required is load size dependent. The actual number can be calculated using the formulas and procedures identified in the respective documents.

The parts of a simple EO validation, assuming qualification of a single device of simple design, are presented below.

Protocol Preparation

AAMI TIR No. 14-19975, titled "Contract Sterilization for Ethylene Oxide," recommends that all qualifications be performed using a written action plan in the form of a protocol. It further recommends that the protocol be reviewed and approved by qualified personnel prior to its execution.

Biological Monitoring

Two types of biological testing are utilized for qualifications. One type is natural product sterility testing and the other is biological indicator sterility testing. Natural product sterility testing is performed after each half cycle to assure the product is rendered sterile by the process as required in USP23. Biological indicator sterility testing when successfully performed demonstrates a 6-log reduction of the biological indicator at half exposure, which yields a

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theoretical 12-log reduction at full exposure (thus the reference to overkill).

Internal Process Challenge Devices (IPCDs), as referenced in the guidelines, are prepared by placing biological indicators in the most difficult to sterilize area of the device. This "sporing" location is selected utilizing data generated during process/product development or by examination by a sterilization specialist who is familiar with the type of device and the sterilization process. The number of IPCDs required is dependent upon the load size (reference 11135).

Additional biological indicators are prepared to be utilized as External Process Challenge Devices (EPCDs). The EPCDs will be placed on the exterior surfaces of the load and will ultimately be used as the routine biological process monitor.

Reference Load Preparation

A reference load is defined in 11135 as "Specified sterilization load made up to represent the most difficult combination of products to be sterilized." Working with the Customer, a reference load will be identified which will assure that the vessel is utilized at its maximum loading, which will result in a challenge of the maximum load density. Once the load configuration is identified, all PCDs (internal and external) are placed on the load along with the product sterility samples and temperature/relative humidity monitoring instruments.

Environmental Preconditioning

Most of the sterilization processes of today start with conditioning of the products to be qualified outside of the sterilization chamber. Preconditioning is usually performed in a room which has been specially designed to heat and humidify the products to a stable internal temperature and moisture content prior to entering the chamber.

The product is placed into the preconditioning room and held for a time (dwell) which has been selected by the EO sterilization specialist to represent the minimum time (+0, -1 hour) which will be allowed during routine production.

Once the preconditioning dwell time is complete, the products are moved to the sterilizer for processing the half or fractional cycle.

Sterilization Processing

- **Fractional Cycle** – The load is processed in a sterilization cycle which has been selected or designed by the EO sterilization specialist to deliver less lethality at a fraction of the routine cycle exposure time, as compared to the cycle which will be used for routine processing.
- **Half Cycle** – The load is then processed in a cycle which has been selected or designed by the EO sterilization specialist to deliver less lethality at one half the routine cycle exposure time, as compared to the cycle which will be used for routine processing.

Heated Aeration

After sterilization, the load is placed in a heated room for additional removal of the residual gases. The rooms are maintained at elevated temperatures and the outgassed residues are continuously removed from the room and scrubbed. The product is resident in the aeration room for a minimum of 6 hours; then it is moved to the sampling area.

Sampling

Biological samples are removed from the load and sent to the laboratory for sterility testing. All biological indicators are aseptically transferred to tubes of growth media and placed into incubation for 7-10 days. All product sterility test units are aseptically transferred to growth media and placed into incubation for 14 days.

Sterility Testing

- **Fractional Cycle (1 each)** – This cycle, if successful, will produce growth of some or all of the biological indicators, yet yield zero growth of the product sterility test units. Biological indicator growth will serve to validate the biological indicator recovery process.
- **Half Cycles (3 each)** – These cycles, if successful, will result

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in total sterility of all IPCDs and product sterility test units. Depending on the resistance of the EPCD, some growth may be observed due to the short duration of the selected exposure time.

- **Full Cycles** – Additional full cycles performed at the routine exposure time will be utilized as part of the qualification process to appraise product functionality, packaging integrity, and EO residues. These will be performed and ultimately be part of the performance qualification data set.

Final Report

A final report will be prepared which contains all data and a summary which identifies the success of the validation process. Approvals for the final report are typically those individuals who approved the testing protocol. A copy of the final report and all data should be maintained on file.

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REFERENCES

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2. United States Pharmacopeia, 31st ed., 2008
3. BS EN 550 – Sterilization of medical devices – Validation and routine control of ethylene oxide sterilization, 1994
4. AAMI Technical Information Report (TIR) No. 14 – Contract Sterilization Using Ethylene Oxide, 2009

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