POINTS TO CONSIDER WHEN AUDITING A TERMINALLY STERILIZED DRUG PRODUCT

by Maxine Fritz

There are two broad methods to produce a sterile drug product, terminal sterilization and aseptic processing. There are various methods of terminal sterilization including moist heat sterilization, dry heat/depyrogenation, irradiation and ethylene oxide. Terminal sterilization is always the preferred method over aseptic processing when possible. However there are situations when terminal sterilization cannot be performed and one must rely on aseptic processing. Aseptic processing does present a higher risk of microbial contamination of product than terminal sterilization. When conducting an audit of the terminally sterilized product process, consider the following factors.

FACILITY AND THE ENVIRONMENT

- ☐ Has the firm performed a risk assessment of its facility and equipment?
- ☐ Does the firm understand the areas of risk as they relate to contamination of drug product?
- ☐ Are the facility, the equipment layout and the air handling system designed and suitable for preventing viable and non-viable contamination?
- ☐ Is the material and personnel flow unidirectional (dirty to clean)?
- ☐ Is there trend data to demonstrate the cleanroom quality?
- ☐ Does the facility have smooth cleanable surfaces? Are the materials non-porous?

SUPPORT UTILITIES

Water systems, in particular the WFI generation equipment and the distribution loops, need careful review.

- ☐ Are there detailed P&IDs/as-built diagrams?
- ☐ Is there a risk assessment that includes slopes, dead legs, non-sanitary fittings and leaks?
- ☐ Is there appropriate sampling at the points of use?
- ☐ Is there inline monitoring for TOC and conductivity?
- ☐ Is there trend data for chemistry, microbiological and endotoxin tests?
- ☐ Are appropriate alert and action levels established?
- ☐ Is there a scheduled sanitization?
- ☐ Is passivation performed when needed and what material is used to passivate?

Air handling units and high efficiency particulate air (HEPA) filters are important to maintain airflow, air filtration and overall air quality.

- ☐ Is the facility controlled and classified?
- ☐ Are the HEPA filters integrity tested?
- ☐ Does the testing include air velocity measurement?
- ☐ Are there appropriate pressure differentials, and temperature and humidity set points?
- ☐ Have airflow pattern (smoke) studies been conducted under dynamic conditions to verify the unidirectional airflow and air turbulence within the critical area where sterilized drug product, containers and closures are exposed to environmental conditions?

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TERMINAL STERILIZATION VALIDATION AND QUALIFICATION

- ☐ First and foremost have all the sterilization processes been validated and is all the equipment such as autoclaves and ovens been qualified?
- ☐ What type of sterilization cycles were used, for example was it bioburden based or an overkill?
- ☐ Does the validation documentation describe the equipment and include the IQ/OQ/PQ data?
- ☐ Are there procedures for revalidation? What is the time period and is it based on risk?
- ☐ Does the validation documentation include empty chamber and loaded chamber heat distribution studies?
- ☐ Was there an identified worst case load?
- ☐ Were Biological Indicators (BIs) used to validate the cycles?
- ☐ What type of indicator was used?
- ☐ What organism was used (genus and species) and is it appropriate for the type of sterilization?
- ☐ Is there a verifiable spore count and what is the approximate D-value of the BI?
- ☐ How many BIs were used per sterilization load?
- ☐ Are there any worst case locations and were the BIs placed in these locations?
- ☐ Is there a diagram of the distribution of the BIs in the loading pattern used?

Please note there are many other considerations when auditing a terminally sterilized drug product and many other issues to consider for an aseptically processed drug product that are not covered above, including having a solid PQS, which we will discuss in our next Journal.

If you need assistance or have questions, please contact me at **mfritz@nsf.org** or at **+1-202-828-1585.**

ABOUT THE AUTHOR

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