



Environmental Monitoring of Manufacturing Processes

The Basics of Monitoring your Manufacturing Environment

To be in compliance with current Good Manufacturing Practices (CGMP) the environment in which a Medical Device is manufactured must be monitored. Several factors are specifically detailed; competent individuals must be able to define the critical areas of manufacture, compile and interpret lab results and advocate a system in which the results are trended. In addition, there must be a program developed and followed for routine (i.e. weekly, monthly, semi-annually, etc.) monitoring of critical areas of manufacture. It is necessary that data is obtained from a laboratory that has adequately trained personnel, calibrated instruments and properly prepared media. And finally, limits should be established for significant drifts or rises in the number of colony forming units found in the environment (alert & action levels).

These Action and Alert Limits should be established after sufficient data is accumulated (ideally at least 4 season changes or 1 calendar year). It is then possible to review and assess a typical range of growth and to assign a number that would flag the attention of the reviewer that there may be either a potential drift in the integrity of the manufacturing process, or an actual outlying trend. Written procedures outlining the steps to be taken should alert or action levels be indicated must be available. Possible corrective actions may include a structured cleaning procedure for critical areas of the manufacturing line and/or a more rigorous cleaning and "gowning" procedure for personnel on the manufacturing line as well as characterization of the recovered organism(s). Characterization of the organism may include gram morphology, colony morphology, or organism identification.

The action and alert limits must be reevaluated periodically to assure the levels are still relevant. These limits should be closely watched even when the manufacturing process includes terminal sterilization.

Methods for Monitoring

The methods most commonly followed are:

Air Sampling:

It is possible to monitor the viable particulate in the environment by means of an air sampling instrument. There are several different types of these instruments on the market, such as the Surface Air System (SAS) and Reuter Centrifugal Sampler (RCS). The air is drawn through the instrument depositing particles onto the agar in either plated or strip form.

Settling Plate:

A prepared media plate, appropriate to the type(s) of organisms of interest, is opened for exposure to the manufacturing process in progress for a specified amount of time. The plate is then covered, incubated and analyzed. This type of sampling is more suitable for qualification/characterization of any recovered organisms rather than quantification.

Surface Sampling:

Two ways of monitoring the surface of a particular area of manufacture are by means of a culture swab and/or a contact media plate. The culture swab is generally used in areas where full contact cannot be made by an agar plate (e.g. crevices between two components, inside a cylindrical drum, etc.). The area is wiped by the swab and placed back into a self contained tube, usually containing a breakable capsule full of transport media that allows the swab to stay moist, but will not encourage or inhibit the growth of any microorganisms present. The entire unit is then sent to a Microbiology lab for plating and analysis. Another process to evaluate the surface of a manufacturing area is by way of a contact plate. A contact plate is nothing more than a Petri dish containing an appropriate microbial media that extends above the lip of the Petri dish to facilitate contact with a surface. The plate is opened and the gently placed onto the surface to be evaluated. It is then lifted, covered, incubated and analyzed.

Collected environmental samples should be submitted to the test facility on ice or cold packs via an overnight courier for immediate analysis. Incubation parameters range from a minimum of 3 days @ 30 – 35° C for a total microbial count, to a minimum of 5 days @ 20 – 25° C for yeasts and/or molds. Colony forming units (CFU) found on the plates are then counted and reported. Characterization of the recovered organisms can then be performed.

Water Monitoring

USP <1231> WATER FOR PHARMACEUTICAL PURPOSES requires any water, used in the production of a drug substance or as a component of a finished product, to meet USP Purified Water standards. Water systems that treat source or feed water for this purpose must be validated to assure proper control against microbial contamination. The system must be quantitatively monitored following a routine schedule to assure that an approach of microbial levels to the established alert and/or action limits will be detected.

The testing that should be conducted on water samples taken at critical points of contact within the manufacturing line include USP Purified Water Monograph (Total Organic Carbons and Conductivity), Heterotrophic Plate Counts (microbial levels), and an In-Process LAL test.

USP Purified Water Monograph:

The two tests that make up the Monograph are the Total Organic Carbon (TOC) and the Conductivity tests.

The Total Organic Carbon measurement is intended to determine the organic chemical content of the water produced by your water system. Because many plastics contain leachable organic compounds (un-reacted monomers, plasticizers, etc.), it is recommended that samples be collected in glass containers which have been cleaned according to USP <1051>. Sample containers should have screw top closures lined with PTFE. A minimum of 50mL is needed for analysis.

The Water Conductivity measurement is intended to determine the dissolved solid content (specifically solids which are ionized in solution such as ammonium, chloride, sodium, potassium, etc.) of the water produced by your water system. A minimum of 150mL should be submitted in plastic for analysis.

Heterotrophic Plate & Filter Counts:

The Heterotrophic Plate Count is designed to determine the number of microbial contaminants found in your water supply at a given port within the water system. The result is calculated in Colony Forming Units (CFU) and can be reported in /mL, /10mL and/or /100mL dilutions. The USP limit for Purified Water is 100 CFU/mL. (Drinking water has a limit of 500 CFU/mL and Water for Injection has a limit of 10 CFU/100mL.) It is recommended that a minimum of 120mL is submitted for analysis to insure that 100mL can be tested.

In-Process LAL:

Endotoxins are lipopolysaccharide complexes that occur in the cell wall of gram negative bacteria. They are pyrogenic, and may cause chills, fever, or other adverse symptoms depending on the bacterial species and the health of the infected person.

Because water can be a major contributor of endotoxin to pharmaceutical preparations and finished medical devices, it is necessary to monitor the levels of endotoxin in water when it comes in contact with or is a component of a medical device or used in a pharmaceutical preparation. If the finished product fails the Bacterial Endotoxin Test, it is nearly impossible to reduce the level of endotoxin without causing detrimental effects rendering the product unacceptable for use.

References:

Journal of Parenteral Science and Technology; Technical Report No. 13, Volume 44 #S1 (1990); Fundamentals of a Microbiological Environmental Monitoring Program;

USP <1116>, Microbiological Evaluation of Clean Rooms and other Controlled Environments

USP <1231> Water for Pharmaceutical Purposes

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