High Efficiency Particulate Air (HEPA) Filters in Sterile Pharmaceutical Manufacturing

An essential element in ensuring aseptic conditions is the maintenance of HEPA filter integrity. Integrity testing should be performed at installation to detect leaks around the sealing gaskets, through the frames or through various points on the filter media. Thereafter, integrity tests should be performed at suitable time intervals for HEPA filters in the aseptic processing facility. For example, such testing should be performed twice a year for the aseptic processing room. Additional testing may be needed when air quality is found to be unacceptable or as part of an investigation into a media fill or drug product sterility failure. Among the filters that should be integrity tested are those installed in dry heat depyrogenation tunnels commonly used to depyrogenate glass vials.

One recognized method of testing the integrity of HEPA filters is the use of a dioctyl phthalate (DOP) aerosol challenge. However, alternative aerosols may be acceptable. Poly-alpha-olefin can also be used, provided it meets specifications for critical physicochemical attributes such as viscosity. Some alternative aerosols are problematic because they pose a risk of microbial contamination of the environment being tested. Firms should ensure that any alternative does not promote microbial growth.

An intact HEPA filter is capable of retaining at least 99.97 percent of particulates greater than 0.3 microns in diameter. It is important to ensure that the aerosol used for the challenge has a sufficient number of particles of this size range. Performing an integrity test without introducing particles of known size upstream of the filter is ineffective for detecting leaks. The DOP challenge should introduce the aerosol upstream of the filter in a concentration of 80 to 100 micrograms/liter of air at the filter's designed airflow rating. The downstream side of the filter is then scanned with an appropriate photometer probe at a sampling rate of at least one cubic foot per minute. Scanning should be conducted on the entire filter face and frame at a position about one to two inches from the face of the filter.

This comprehensive scanning of HEPA filters should be fully documented. While vendors often provide these services, the drug manufacturer is responsible for ensuring that these essential certification activities are conducted satisfactorily. A single probe reading equivalent to 0.01 percent of the upstream challenge should be considered as indicative of a significant leak and

should result in replacement of the HEPA filter or perhaps repair in a limited area. A subsequent confirmatory re-test should be performed in the area of any repair.

There is a major difference between filter integrity testing and efficiency testing. The purpose of regularly scheduled integrity testing is to detect leaks from the filter media, filter frame and seal. The challenge is a polydispersed aerosol usually composed of particles ranging in size from one to three microns. The test is done in place and the filter face is scanned with a probe; the measured downstream leakage is taken as a percent of the upstream challenge. The efficiency test, on the other hand, is a test used only to determine the rating of the filter.

HEPA filter integrity testing alone is not sufficient to monitor filter performance. This testing is usually done only on a semi-annual basis. It is important to conduct periodic monitoring of filter attributes such as uniformity of velocity across the filter (and relative to adjacent filters). Variations in velocity generally increase the possibility of contamination, as these changes (e.g., velocity reduction) can have an effect on the laminarity of the airflow. Airflow velocities are measured six inches from the filter face or at a defined distance proximal to the work surface for each HEPA filter. For example, velocity monitoring as frequently as weekly may be appropriate for the clean zone in which aseptic processing is performed. HEPA filters should be replaced when inadequate airflow (e.g., due to blockage) or non-uniformity of air velocity across an area of the filter is detected.
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