

Application Note

Drug Product-Based Integrity Testing Establishing a Product/Filter Test Minimum Value

Millipore provides minimum integrity test specifications for filters wet with standard wetting fluids: water for hydrophilic filters and alcohol for hydrophobic filters. These wetting fluids are ideal for pre-use integrity testing; however, after use the filter is wet with the process fluid (drug product) it was used to filter. Most drug products have a surface tension that is different from that of the standard wetting fluid and in most cases this alters the integrity test results. Delays in production and product release caused by false test results can be minimized by drug product-based integrity testing. Likewise, process fluid that tends to increase bubble point may cause a filter, which would not have met minimum specification, to pass.

Millipore's experience has proven that determining product bubble point values by simply using a surface tension ratio and mathematical calculation is unacceptable. Variables, such as the wetting contact angle, may also affect integrity test values—physical integrity tests must be performed to determine the product-based value.

The minimum acceptable integrity test value for filters wet with product can be established by determining the water/product integrity test ratio. Millipore Validation Specialists perform water and product integrity testing on filters to establish the ratio. The ratio is then used to calculate the minimum acceptable integrity test value for filters wet with process fluid.

- Determine the correct testing for your process
- Provide test protocols, reports and customized test systems when necessary
- Maintain raw data files
- Ensure confidentiality



A standard test protocol is submitted to the client. When both Millipore and the client sign the project specific test protocol, testing begins. A standard report summarizing testing data is submitted to the client at the completion of testing.

Millipore's Validation Sciences Laboratories Service Specialists are committed to performing testing at validation labs in the U.S., Europe, India and Japan. Millipore welcomes and encourages client audits of our worldwide laboratory facilities. Let Millipore's years of filtration and process optimization experience save you time and resources.

REGULATORY COMPLIANCE

Filter integrity testing is a critical step in the manufacture of sterile drug products and is required by regulatory bodies worldwide. The United States Food and Drug Administration's Guideline on Sterile Drug Products Produced by Aseptic Processing recommends post-use integrity testing to check for leaks or filter damage. PDA's Technical Report 26 further outlines the test methods. Millipore's testing is performed in compliance with these guidelines.

TEST PROCEDURE

Testing is conducted using small volumes of process fluid and Millipore sterilizing-grade, 47 mm membrane discs or filter devices. Testing is designed to model key process parameters such as process temperature, wetting fluid temperature, and type of test gas used. The number of process fluid lots and filter lots is decided by the client. Upon completion of testing, data is analyzed to ensure stable and reproducible results among the test replicates. The results of the Drug Product-Based Integrity Testing will provide the customer with a starting point to gather and compare product bubble point data during their manufacturing process.

WHY INTEGRITY TESTING IS IMPORTANT

To ensure product sterility and regulatory compliance, membrane filters must be integrity tested after filtration of a drug product. Integrity testing ensures that the correct pore size filter was used, the filter was installed properly, and the filter was defect free. Integrity testing is highly dependent on the physical characteristics of the wetting solution, and even small changes to the test solution can substantially alter integrity test results.

When physical characteristics of the process fluid alter integrity test results, there are two options available. The process fluid must either be completely flushed out to fully

wet the membrane with a solvent of known integrity test values, or the effect of the drug product on integrity test results must be determined. Completely flushing the process fluid from the membrane can be time consuming and costly. Additionally, some components may bind to the membrane regardless of the volume passed through the filter, and not readily flush out.

WHEN PRODUCT BASED INTEGRITY RATIO TESTING IS REQUIRED

- When product is not or can not be rinsed off of the filter prior to measuring the integrity value
- When the filter is sterilizing grade with a sterilizing claim and post-use integrity is critical

WHAT YOU NEED TO KNOW TO BEGIN

- How many lots of process fluid are available for testing, and when?
- Do you have an MSDS for the candidate test solution?
- Is this a controlled drug? If so, what are the classification and code?
- What is the room temperature and fluid temperature when the integrity tests are conducted?
- What is the test gas?
- What are the integrity tests used for batch release? Bubble point? Diffusion? Both?

ORDERING INFORMATION

Contact your local Validation Sciences Laboratory for a current request form. The scope of your project will be determined by the request and process conditions. A catalog number will be assigned accordingly.

To request integrity testing or to get information on other validation services, call your Millipore Applications Specialist or the Millipore office nearest you.

In the U.S. and Canada, call toll-free
1-800-MILLIPORE (1-800-645-5476)

In Europe call: **+33 (0) 390 469898**



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