BIOTECH

Application Note

USD2235d

How to Select the Right Filter Integrity Test Instrument

Contents

1 Overview

Filter integrity testing, from its origins in the 1970s, has undergone significant changes over the last 40 years as industry needs, and the evolution of regulatory expectations have pushed boundaries to reduce risk and increase patient safety. Our founder, Dr Pall, was a pioneer in filter integrity testing, having developed what he referred to as the 'Forward Flow' test in 1973. Prior to this and throughout the 1970s filter integrity testing was just a manual bubble point test for a few critical use filters, using a pressure gauge.. These initial manual tests paved the way for the first purpose-built integrity test instruments, developed in the 1980s specifically for the pharmaceutical market. The introduction of FDA guidance and European Good Manufacturing Practice (GMP) (regulators) in 1987 of mandatory integrity testing of critical use filters, accelerated the need for high performance automated test equipment.

By the mid-to-late 90s recommendations for filter integrity testing by the regulatory bodies had expanded. US regulators recommended integrity testing of vent filters in place, and new EU guidelines for GMP were published: Medicinal Products for Human and Veterinary Use (Annex 1) requiring that the integrity of a sterilizing grade filter is tested pre-use and post-sterilization (PUPSIT). This is a subject that still generates some discussion more than 20 years later.

As paper batch records have moved towards electronic, concerns over data integrity have been addressed and improved through Good Automated Manufacturing Practice (GAMP®) guidelines, and increased clarification by the FDA in the form of 21 CFR part 11. Currently, some models of filter integrity test instruments can offer secure data management and data transfer, and confidence that a static filter integrity test result is a true result that cannot be altered.

This guide will help you select the right integrity test instrument, including criteria that will allow accurate filter integrity testing that is fully compliant to current regulations.

2 Design

2.1 Ease of Use

Ease of use is often cited by operators as the primary factor that affects their selection of an instrument. This is a significant aspect to consider when deciding on the right choice for any application. Automated instruments that have intuitive navigation across a well-designed human machine interface (HMI), tend to be quick to learn, quick to adopt, and reduces deviations by minimizing operator errors. Easy to use instruments also simplify the training and routine re-training burdens demanded in any GMP process, saving operator time, and reducing training costs. Ideally instruments will take up a small footprint and will be light and portable to aid flexibility across multiple test locations within a facility.

TIP 1: *If possible, obtain a demonstration instrument for evaluation and allow a cross-section of users to experience the instrument and perform each of the tests that the instrument is expected to run. If a knowledgeable operator requires more than basic direction to perform the tests, this may be an indication that the instrument takes some time to master and may continually present usability challenges throughout its lifetime.*

TIP 2: *Ask about options to reduce transcription errors by using technology such as barcode readers for the entry of test data.*

2.2 Environment of Use

Integrity test instruments might be used in a wide variety of settings ranging from uncontrolled plant areas to highly controlled and monitored cleanrooms. The physical design of the instrument should be suitable for each of the environments that it may be used within. Best in class equipment will have design features to support the use in clean environments. These features may include an absence of internal ventilation that could generate particles, or the instrument being dust and splash proof; perhaps with appropriate IP ratings that support the external cleaning requirements, common in the most challenging environments.

2.3 Reliability

Most integrity test instruments are exposed to liquids that might contaminate their internal components. If not managed properly, this may lead to increased service costs, or cause a loss of function or accuracy of the instrument over time.

Best in class equipment will have methods to avoid process liquids draining back into the instrument and may also utilize an internal diagnosis program to check the critical hardware performance at regular intervals. This is executed to highlight any potential issues before using the instrument in critical tests.

TIP 3: *Ask the manufacturer for their recommendations on how to apply additional process controls through good instrument design and test installation practices.*

3 Function

3.1 Supported Tests

In certain environments, some instruments could be better suited to particular types of integrity test than others. In general, there are three types of filter integrity test: forward flow (diffusive flow), bubble point and water intrusion.

TIP 4: *Ensure that the instrument you are planning to purchase is capable of each of the tests that you wish to perform or may wish to perform in the future.*

Best in class instruments may also allow for the application of the same measuring technology to other pneumatic tests such as leak testing of various fixed volume vessels or systems and the installation testing of single-use systems. Additional functionality may provide further opportunities to control future process risks with no further investment.

TIP 5: *Obtain a demonstration instrument for evaluation and run each of the tests that you expect to perform.*

3.2 Accuracy

As the accuracy of any instrument increases, there is a decrease in process risk resulting from the potential for a filter integrity test to provide a false result. Both false passes and false failures impact upon either the process safety or efficiency and are highly undesirable.

The claimed accuracy of the integrity test instrument might vary from 3% to as much as 10%, for different measurement ranges.

Underpinning the accuracy claim of any instrument are its calibration methods. Should you wish to confirm those claims, comparisons can be performed using gas flow measurement references that are typically available from 1 mL/min to 1000 mL/min. They can be used to

confirm the performance for diffusive flow testing. No equivalent references exist for the measurement of the bubble point, therefore a claim for accuracy based on reproducible measurements cannot be given.

TIP 6: *Find out what safeguards are provided to prevent false pass results and false failures for any instrument you are considering. For example, methods are available to assure that the differential pressure over the tested filter is not impaired by elevated pressure on the downstream side of the filter, or to prevent a pass result if the integrity test is run against a closed valve.*

TIP 7: *Ask if there are any devices that might assist in reducing any residual risks by identifying issues before they lead to batch deviations. Consider using a flow check device as a way to monitor accuracy between calibrations.*

3.3 Speed

Some flow measurement technologies, when coupled with validated algorithms, may be able to shorten the filter test times without any compromise of the measurement accuracy. Latest instrumentation models offer faster network integration and up to 20% reduction in test time when compared with older models. These shorter test times can release valuable resources for other process tasks and speed the progress of process operations.

TIP 8: *Compare how quickly each instrument performs each test, especially those you expect to do routinely. While comparing test speeds, also check that instruments that offer the highest speed of testing still maintain the test accuracy.*

For users that need to test large numbers of filters, even more time can be saved by using instruments and extensions that can support the testing of multiple filters without the operator returning to the instrument during the testing.

TIP 9: *Check to see if the instrument can be used to support the testing of multiple filters without increasing the number of units that require calibration.*

4 Compliance

4.1 Validation

According to GAMP5 guidelines, integrity test instruments are typically rated as software category 3 and hardware category 1. Test instruments should be manufactured in accordance with the latest industry standards and designed with FDA approved components. They should also possess technological controls required for use in a 21 CFR Part 11 compliant environment.

Integrity test instrumentation are defined as ‘off-the-shelf’. For such instruments a comprehensive validation/qualification package prepared by the vendor can significantly reduce the qualification efforts for the user.

TIP 10: *Look for tools and resources that the manufacturer can provide to assure that the instrument will be successfully validated - ask what documentation is available.*

4.2 Calibration

Regular calibration of instrumentation is an integral part of GMP compliance. However, it can be easily overlooked when focusing on the design and function characteristics of an integrity test instrument.

TIP 11: *Find out how the instrument is calibrated. For integrity test instruments which measure pressure and flow, this should be a calibration against pressure and flow references in order to assure accurate results.*

4.3 Data Safety and Transfer

For electronic records the equipment needs to offer technological controls required for operation in a 21 CFR Part 11 compliant environment that exhibits features required for data integrity and electronic records/electronic signatures. An increasing need for assurance of data integrity and electronic audit trails that confirm 'static' test records with date/time of test and electronic signatures, is essential.

TIP 12: *Look out for instruments that have been designed using ALCOA Plus principles to ensure data security and protection is observed, and the highest product quality and patient safety is maintained.*

- *Attributable: Controlled access records the user, time, and date for each test, creation/modification of tests and configuration and date/time changes, all of which become part of the record audit trail.*
- *Legible: all parameters defining a test and all metadata are included in the test results so the raw data can be understood. This allows a clear picture of the sequencing steps or events in the record.*
- *Contemporaneously recorded: test results are recorded as they are generated and completed.*
- *Original: test results are the first captured data and do not require recalculation, and only electronic signatures with comments can be added.*
- *Accurate: test results are based on flow measurements that are properly calibrated against traceable pressure and flow references and the system verifies that the screen display, print result and data contents all match.*
- *Complete and Consistent: test results are static records. All data are available to view with nothing deleted. The test result is complete and cannot be modified after the result is stored . Test results are stored chronologically with date and time.*
- *Enduring: test results are recorded with a time stamp, and each test is linked to the serial number of the instrument, which has the time synchronized with the time of the host PC or relevant server. A continuous test counter also maintains the sequence of tests independent of the time stamp.*
- *Available: configuration, test programs, user data and test results can be easily exported to a computer network or an external flash drive for long-term storage.*

4.4 After-Sales Service and Support

Access to agile, efficient, and effective service support is critical for a best in class instrument to keep it in top operational condition, optimizing its accuracy and productivity throughout its service life.

TIP 13: *Challenge the manufacturer to see if they have well-trained and certified service technicians as well as sufficiently equipped facilities to support installations, annual calibrations, re-qualifications, maintenance, software upgrades and other service procedures, in addition to finding and fixing the root causes for out of limits tests.*

TIP 14: *Ensure the recommended maintenance servicing schedule is followed to protect the instrument, increase its day-to-day efficiency as well as elongating its service lifetime.*

4.5 Training

Look at the practical and theoretical operator training that can be provided to support your in-house training programs. With 4.3% batch failure attributed to human error, sufficient training in instrument operation is essential to reduce risk and contribute to operator compliance. Train the trainer courses should also be available to pass on knowledge effectively throughout the facility.

TIP 15: *Ask the manufacturer if they have an e-training platform that will support real-time training and continuous learning with qualification records that are saved, certified and traceable.*

TIP 16: *Ask your instrument supplier if they can provide virtual reality training for a more in-depth experience.*

5 Automation

5.1 Protocols

In an age of multiple digital pathways and interfaces, ensure the test instrument meets current industry communication standards with regard to automation protocols. Typical requirements are ProfiBus, ProfiNet, DeviceNet and OPC UA for control levels to other systems, SCADA for transmitting results into central storage, ethernet for downloading results for backup or archiving, and manufacturing execution systems (MES) for remote control and data collection

TIP 17: *Check the test instrument has multiple interfaces to enhance flexibility and reduce both operational time and costs.*

5.2 Customization

Instrumentation should be designed with some degree of flexibility and adaptability to meet your unique application set-up.

TIP 18: *Review an instrument's capabilities and degree of flexibility before purchase, and if needed discuss options for customizing your filter integrity test instrument to meet your present and future needs.*

5.3 Third-Party References

Obtain references and published reports describing the instruments. Seek out other users in your company (perhaps in a different location), who have knowledge and experience they can share.

TIP 19: *Ask if the manufacturer can connect you with some existing instrument users.*

By taking all of the above criteria into account, and obtaining feedback from other users, you will be on the right track to choose the best filter integrity test instrument for your process.

Pall is confident that the Palltronic® range of integrity test instruments is the right choice for your process. If you wish to investigate this further, we look forward to answering any questions you may have.

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