Addressing Regulatory Requirements for Filter Integrity Testing

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Filter integrity is a fundamental element of sterility assurance during production of biopharmaceutical and vaccine products (**1**). Integrity test results are a key foundation for drug lot release, so any external element that could affect their reliability must be viewed as a critical issue. But when should a filter integrity test be performed?

Although postuse filter integrity testing has been a worldwide regulatory requirement for many years, preuse integrity testing is subject to regional variations. The new EMA Annex 1, that has been reviewed by the US Food and Drug Administration (FDA), the World Health Organization (WHO) and the Pharmaceutical Inspection Cooperation Scheme (PIC/s) is expected to come out in 2020 (**2**). Thus, it is expected to align most regulatory requirements not only for when to perform filter integrity testing, but also on additional considerations such as quality risk management (QRM) throughout the entire pharmaceutical process. Therefore, it should include QRM for filter integrity testing. A QRM approach already should be in place for companies operating according to the International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline Q9 (**3**), and the future Annex 1 will emphasize its importance further. Other widely used guidelines such as data-integrity guidances from the UK Medicines and Healthcare Products Regulatory Agency (MHRA) and the US FDA (**4, 5**), along with recommendations from the Parenteral Drug Association (PDA), also align most regulatory bodies on this subject.

Figure 1: Sartocheck 5 Plus filter integrity tester

In addition to the above standards and guidelines, regulators also have expectations related to health, safety, and the environment (HSE). These are intended — among other things — to prevent operator accidents, especially when processes such as filter integrity testing involve pressurized gases and inflammable liquids.

The performance of filter integrity testing devices often is taken for granted. Many devices from different suppliers provide reasonable accuracy and reproducibility. Where they differ is in their compliance (or lack thereof) with the above-mentioned regulatory expectations in terms of data integrity, QRM, and HSE. End users always should request information on such compliance before purchasing a filter integrity testing device. Once such a device is installed, mitigation strategies to use it within those guidelines can have only limited efficiency.

Because Sartorius Stedim Biotech (SSB) is aware of the regulatory issues surrounding filter integrity testing, the company has introduced its Sartocheck 5 Plus filter tester (Figure 1). The test performance and accuracy of this device is based on its well-established predecessor, the Sartocheck 4 Plus filter tester, which was the industry standard in filter integrity testing for many years. As detailed herein, the new product addresses the above regulatory issues and provides ease of use in compliance with industry standards such as for easy log-on with network credentials (LDAP), automation, and data transfer. Therefore, it sets a new standard for filter integrity testing devices in the biopharmaceutical industry.

PRODUCT FOCUS: ALL BIOLOGICS

PROCESS FOCUS: DOWNSTREAM PROCESSING

WHO SHOULD READ: QA/QC, MANUFACTURING

KEYWORDS: FILTRATION, RISK MANAGEMENT, LOT RELEASE, REGULATORY COMPLIANCE, DATA INTEGRITY, AUTOMATION

LEVEL: INTERMEDIATE

Data Integrity

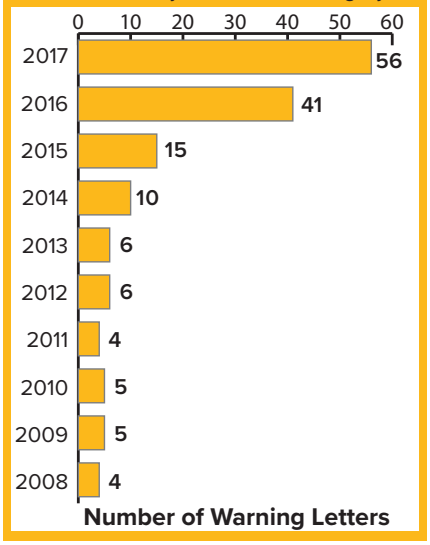
According to the PDA, data with "integrity" are accurate and contain no errors or editing without documented amendments. Such information is attributable (listing who acquired it) and made available for review, audit, or inspection over a record's lifetime. These data also are complete and consistent with all elements of each record and are dated or time-stamped in an expected sequence of events.

Because filter integrity test results are fundamental to the release of a final drug product, their integrity must not be seen as simply an information technology (IT) problem, but rather as a global business risk that could jeopardize a company's drug manufacturing activities (and more critically, patient health) if not fulfilled to the highest standards. Devastating malware incidents and the continuing threat of computer-virus "infections" have created an urgent need for data protection and security. The completeness, consistency, and accuracy of data throughout each product's entire life cycle are critical aspects of regulatory compliance in all systems that generate, store, and retrieve information. The FDA issued guidelines on how to maintain data integrity in 2016 (**6**), and the number of FDA form-483 warning letters related to data integrity has increased dramatically (Figure 2), illustrating how seriously the agency views this subject.

The customized Linux operating system and write-protected root-file system of the new filter-integrity device have been designed in accordance with the highest demands for data integrity. They use unalterable data formats for test results and audit trails and protect against malware and virus infections to ensure preservation of data integrity.

Under the "four-eyes principle," test results must be approved by at least two people. This forms the cornerstone of every quality system: e.g., good manufacturing practices (GMPs), good laboratory practices (GLPs), and standards such as 17025 from the International Organization for Standardization (ISO). The Sartocheck 5 Plus device uses this principle to provide users with the option to enhance test result reliability and data validation. Using the device's tailor-made user- and role-management systems, a person with approval rights can be identified to facilitate delegation of authority, increase transparency, and ensure accuracy/traceability of results.

Figure 2: Numbers of FDA warning letters issued in recent years for data integrity



Quality Risk Management

Operator training is mandatory for compliance with GMPs according to ICH Q9. It also reduces the occurrence of errors. Assessing the potential severity of operator errors is necessary to determine what remedial actions will be required. Training of quality assurance (QA) staff improves detection of operator-related errors, but any deviation they detect will have occurred already — and some deviations could go undetected.

QRM is more than just a regulatory requirement; it must be implemented to ensure patient safety. Because filter integrity testing is an essential step in drug lot release, a false-passed integrity test result (one that conforms to specification although the filter has been damaged) can jeopardize the health of patients. A false-failed test result (when an intact filter fails testing) requires quarantining a drug lot, which can have a negative financial impact on the drug manufacturer or, even worse, create a drug shortage that would compromise patient health outcomes.

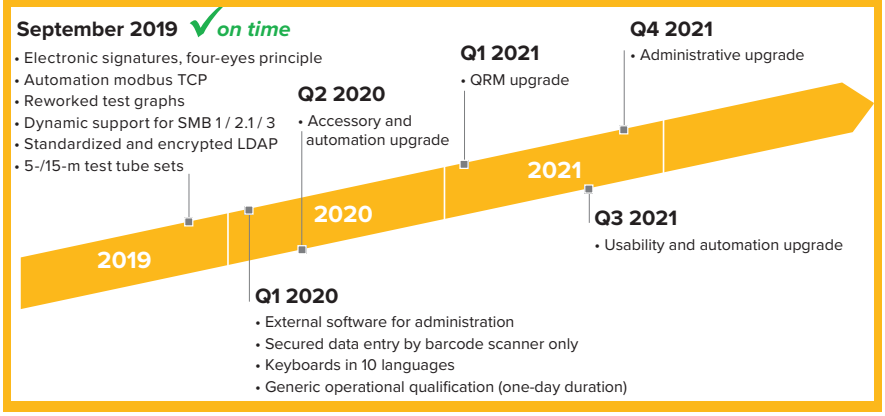
With program-specific parameters, the Sartocheck 5 Plus filter tester allows automatic detection of testing anomalies and operator errors both during or in advance of a test. That prevents time-consuming and costly deviations, potential drug recalls, and warning letters. A supplied comprehensive failure mode effects analysis (FMEA) can identify conditions that might generate false passes or fails, thus indicating to operators where existing controls or measures will require further strengthening. The FMEA also can analyze risks to operators when compressed gas is used for testing the device internally and externally and when moving such gases from one location to another. This documentation also includes directives and real examples for setting program-specific safety parameters to prevent false passed and failed.

Figure 3: The bright screen of the Sartocheck 5 filter tester is readable from all angles.

Usability

Easy connection with network credentials (through LDAP), straightforward data transfer, and automation capabilities are basic requirements for modern integrity testing devices. An optimized user experience speeds up process workflows because intuitive guidance and ease of use speeds device set-up and reduces operator errors. By combining the high-quality touchscreen's unique viewing angle (Figure 3) with an intuitive user interface, a logical menu structure, and simple data-entry options with a barcode scanner, the filter-integrity tester is designed to ensure that testing will be as straightforward as possible. These features enable simple programming of test parameters and QRM enhancements while reducing operator-input errors, making the device suitable for use in GMP production environments.

Figure 4: Roadmap of future developments for Sartocheck 5 Plus filter tester; TCP = transmission control protocol; SMB = server message block protocol; LDAP = lightweight directory access protocol; QRM = quality risk management



Health, Safety, and Environment

Regulatory requirements play an important role in HSE, and managers must identify and understand relevant HSE regulations. Their implications must be communicated to corporate executives so that a company can implement suitable measures to ensure the health and safety of employees and the external environment.

Filter integrity testing uses compressed gas, regularly subjecting a test setup to pressures as high as 4-bar gauge (58-psi gauge). Opening a pressurized system exposes operators to obvious dangers, so all necessary means to prevent accidents must be put into place. Having a large, bright screen that is readable from all angles is one way in which the test system contributes to operator safety. Users will notice more readily when issues arise with their filter integrity and thus correct them before a situation becomes hazardous.

Also, filter integrity testing often involves flammable alcohol. For example, if an integrity test fails, the PDA recommends retesting (**1, 7**). Some nine out of 10 failures are attributable to improper wetting, so the third and final test should be performed after wetting a membrane with, for example, 60–70% isopropyl alcohol (IPA). If that test fails, a filter should be deemed nonintegral and an investigation should be performed. To ensure safe operation even when alcohol is used for wetting, Sartocheck 5 Plus devices are certified for use in explosion hazardous areas to all major global standards: e.g., those set by ATmospheres EXplosible (ATEX), the International Electrotechnical Commission Explosive Atmospheres (IECEx), and the Factory Mutual Research Corporation (FM). Users have the option to add an accessory kit for efficient external venting to prevent liquids and aerosols from contaminating the internal pneumatics or the operator environment.

Another HSE issue is assurance of operator safety in relation to potential microbial and chemical contaminants. Compatible with all current cleaning agents and vaporized hydrogen peroxide (VHP) for efficient rotating cleaning procedures, the new filter tester complies with this HSE need as well.

Roadmap

SSB has a development roadmap in place (Figure 4) for the Sartocheck 5 Plus filter tester that includes innovative, patented or patent-pending software innovations, and hardware solutions that ensure ongoing optimal data integrity and improved QRM, HSE, and usability. Software upgrades are included in the cost of the device and come with clear risk assessments. End-user administrators can perform these upgrades easily once the QA and IT departments approve their implementation.

By combining an intelligent approach to QRM with secure data integrity, intuitive usability, and minimized HSE risk factors — along with a roadmap of future developments — the Sartocheck 5 Plus device meets regulatory requirements for filter integrity testing. That makes it suitable for use in today's and tomorrow's demanding biopharmaceutical GMP environments.

References

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