Background
Gressett, et al of Alcon Laboratories was the first rapid sterility test method approved by the Center for New Drugs (CDER) of the US Food and Drug Administration (1). This test method utilized the ScanRDI technology. This method was attractive for drug testing since the sterility test could be completed in approximately four to six hours, basically a same-day sterility test. Use of this technology allowed manufacturers of aseptically filled products to realize the shortened sterility test incubation time similar to the timing available for those products subject to parametric release.

Recently, FDA inspected a compounding pharmacy using the same technology and issued an inspection report. There were numerous observations, many of which were specifically related to the method and use of the ScanRDI. Specifically, FDA noted that the system was not properly validated, and they provided comments on the validation conducted. These observations are discussed in more detail in this paper. It should be noted that the ScanRDI is also known as the ChemScan or ChemScan RDI in some geographic locations. Review of this paper is important to identify regulatory concerns with the implementation of the ScanRDI as an alternative sterility test method.

The ScanRDI
The ScanRDI (ChemScan RDI) technology is a rapid microbiological method that provides users with the ability to detect microbial contamination for filterable products in a very short time period, without requiring the growth of microorganisms for the detection. Depending upon the test method, results can be obtained in approximately 30 minutes to four hours. This technology is based upon the use of fluorescent cell labeling and laser scanning. It is also referred to as Solid-Phase Cutometry (2). This technology allows for detection of single cells.

Smith, et al. (2010) published results comparing the limits of detection for the sterility test performed using the ScanRDI to the compendial sterility test method (3). Various publications indicate that the technology has been used for the control of process water, release of non-sterile product, environmental control, and sterility testing (1, 2).

FDA Issues Inspection Report
An inspection report was generated for a compounding pharmacy using the ScanRDI technology in Texas. The inspection was conducted in June 2013 (4). A copy of the response to these inspection findings can also be found on the FDA Electronic Reading Room (5).

Some of the observations from this inspection report are provided. Note: Only observations relative to the ScanRDI are included. They may be abbreviated (evidenced by ...) to eliminate redundancy and/or proprietary information (4):

OBSERVATION 1
Laboratory controls do not include the establishment of scientifically sound and appropriate specifications, standards, and test procedures designed to assure that components conform to appropriate standards of identity, strength, quality and purity.
Specifically,
A) There is no validation performed on the Rapid Scan RDI instrument to determine its suitability for use as a sterility test for product that they test.
B) Your firm does not conduct growth promotion on the Trypticase Soy Broth (TSB) and Fluid Thioglycollate Medium (FTM) used in their membrane filtration and direct inoculation sterility tests for drug product as required in the USP <71 > Sterility test
C) There is no suitability testing performed on drug product samples prior or concurrently during membrane filtration sterility testing as required in the United States Pharmacopeia Chapter <71 > Sterility Tests.
D) Your firm does not indicate the number of samples received or required for sterility testing. USP <71 > specifies the number of articles to be tested. While you provide reference to USP <71 > for sample sizes, you do not ensure that your clients are submitting the required number of articles for testing.
E) Your firm has not validated your “plate contamination method” to determine whether it is suitable for its intended use by the customer as a sterility test method.
F) Your firm does not conduct growth promotion on the Tryptic Soy Agar plates used in testing drug product samples for microbial contamination via the TSA (Tryptic Soy Agar) Microbial Plating method.
G) Finished product samples tested for microbial contamination using the Tryptic Soy Agar Microbial Plating Method were not tested for suitability
Deviation from written specifications are not justified.

Specifically,

A) 31 out or 33 Drug product samples were released as were tested for sterility on the SCAN RDI instrument on March 21, 2013. A typical run consists of Quality Control C3 beads, drug product samples, one positive control and one negative control. The positive control used for the run was Staphylococcus aureus; it was run but it was not detected by the machine. Drug product samples that were run on March 21, 2013 via Rapid Scan RDI were passed and released even though the positive control was not recovered or out of specification. No documentation of this deviation was recorded except the printout of results for that day. The SOP [standard operating procedure] for Rapid Scan RDI Quality Control #458, dated 02/22/11 requires an OOS investigation for a failed control. There was no documentation of an investigation, and the results were released with the positive control with no growth. There was no positive control sample included 02/15/2013, and 03/22/2013. Additionally, the positive controls for 03/20/2013, and 06/19/2012 also had positive control with no microbial recovery/no growth.

B) No growth was detected by the machine for the positive control used for testing on January 31, 2013. The SOP for Rapid Scan RDI Quality Control #458, dated 02/22/11 requires an investigation for a failed control. The test results were released based upon the Scan RDI results without the positive control being included in the validation report.

C) The Convenience sterility test method using the Scan RDI was conducted for the March 21, 2013 test run. The convenience sterility test method is described in the Parenteral Drug Association’s (PDA) Technical Report Number 33 (revised) Evaluation, Validation and Implementation of Alternative and Rapid Microbiological Methods (7), and specific validation criteria for this type of testing are provided in USP <1223> (8) and European Pharmacopoeia (Ph. Eur) 5.1.6. (9). Depending upon the validation approach utilized, the USP’s method suitability test (Bacteriostasis and Fungistasis) should also have been conducted either as part of the equipment validation or in a method validation protocol. This validation should have included verification of the equipment itself as well as the methodology.

Completion of validation as described in the documents above would also have included development of standard operating procedures or work instructions that clearly identified the way the test should be conducted. Had these procedures been implemented and followed, this should have resolved issues cited in the observations, such as: the broths used needing to be subjected to a growth promotion test, verification that the correct numbers of samples are obtained for the test method; verification that testing is conducted to ensure that the product formulation does not enhance or inhibit the results obtained; maintenance of the records required in Observation 3; and so forth. Since the ScanRDI uses fluorescence, it is important to ensure that the formulation itself is not fluorescent—for example, the chemical riboflavin autofluoresces. The FDA’s observation includes wording about a plate contamination test method, but insufficient information is provided to clearly understand what this is or how the information is used.

The site also referenced testing being accepted by Certificate of Analysis (COA) from the vendor, but they did not keep copies of these certificates. If data is being accepted via a COA, the firm has a responsibility to maintain copies of these documents.

In the second observation, the site had a requirement to use a positive control of S. aureus when running the system. Numerous samples were tested and released based upon the ScanRDI results without having the positive control meeting the test requirements. The site should have conducted a thorough investigation to determine why the system was unable to detect the positive control organism. No evidence was provided to ensure the system was operating correctly. As such, it is not clear how the test results were released. The site should have an SOP that clearly identifies what to do in the event of a failed control as well as how the test results should or should not be accepted. This would be considered a failed or out-of specification sterility test result. There is guidance for conducting sterility test investigations in the FDA’s Aseptic Pro-
cessing Guidance (10). The test was further complicated on some days by failure to recover the positive control organism when cultured for recovery.

While these observations are generated, it is possible to properly validate and use the ScanRDI for sterility testing in pharmaceutical applications.

Note, the laboratory inspected has a published official response to these inspection items. They are not addressed in this report, but are available for perusal (5).

Conclusion
While the FDA has cited the ScanRDI in this inspection report, all of the observations could have been easily addressed using current industry and regulatory guidance available.

References

About the Author
Jeanne Moldenhauer is Vice President of Excellent Pharma Consulting. She has over 25 years experience in the pharmaceutical and biotechnology industries. She chairs the Microbiology/Environmental Monitoring Interest Group of PDA and is a member of the Science Advisory Board.

Originally Published at: http://www.ivtnetwork.com/article/fda-cites-scanrdi-rmm-inspection-report