Developing a Validation Strategy for Rapid Microbiological Methods

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> "All analytical methods need to be validated prior to their introduction into routine use, and this is especially true for novel technology platforms, such as rapid microbiological methods (RMMs)."

Method validation is the process used to confirm that an analytical procedure employed for a specific test is reliable, reproducible and suitable for its intended purpose. All analytical methods need to be validated prior to their introduction into routine use, and this is especially true for novel technology platforms, such as rapid microbiological methods (RMMs). Because many RMM technologies consist of a combination of instrumentation, software, consumables and reagents, in addition to specific detection, quantitative or identification methodologies, it is important to develop a comprehensive and holistic approach to the validation process to ensure that the entire RMM system is suitable for its intended use. The following sections provide an overview of how to design a meaningful validation program in order to effectively demonstrate that the new RMM is equivalent to, or better than, the existing method you intend to replace.

Initial Activities

Prior to purchasing and validating a RMM, there are a number of due diligence activities that should be undertaken. These may include a thorough understanding of the scientific needs of the RMM, the technical benefits the RMM possesses as compared with the existing method, regulatory impact, economic advantages, and the role of the RMM supplier in terms of providing support during the initial assessment, validation exercises, and most importantly, after the system has been placed in service for routine use.

From a scientific perspective, it is important to understand what technical capabilities are required, including, but not limited to, method sensitivity and specificity (e.g., detection levels and for what types of microorganisms), sample throughput, sample type, automation, data handling and archiving, report management, if the system needs to meet 21 CFR Part 11 expectations, and the required degree of operator training.

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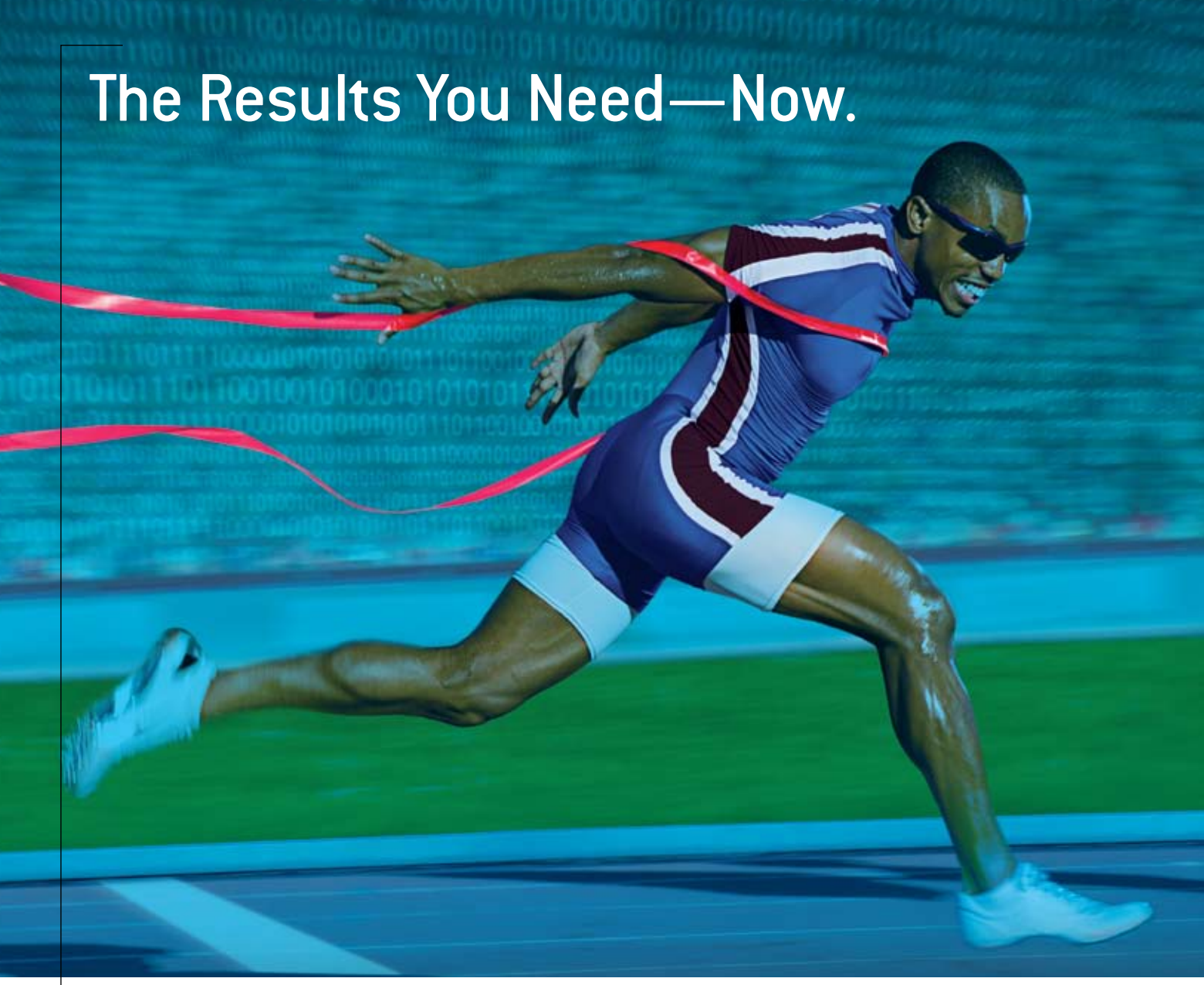

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Proof-of-concept or feasibility testing can also be performed to determine if incompatibilities exist between the RMM and the intended product or test sample(s). These types of studies can also be performed in the event the RMM supplier has little or no data on testing similar product or test materials. This can be accomplished using a rental or loaner instrument, or by sending samples directly to the supplier for evaluation. The data obtained from these initial studies will help with the decision to purchase the RMM and proceed with formal validation activities.

The due diligence process also involves a review of existing regulatory commitments and whether implementing the RMM will result in significant changes that will require a formal submission. Additionally, a financial assessment of the costs (and cost savings) associated with the purchase, validation and implementation of the RMM should be performed.

Finally, the selection of a RMM supplier is just as important as the RMM itself, and it is important to have a thorough understanding of the supplier's technical capabilities and their ability to support each phase of the validation process as well as continuing assistance once the RMM is placed into service.

In summary, the initial assessment of a RMM should include a comprehensive scientific, regulatory and business due diligence review, in addition to matching the appropriate technology with the desired microbiology application. It is not uncommon in our industry to find firms that have purchased a RMM system and spent considerable time, resources, and expense in validating the instrumentation and method only to find, at a later date, that the technology is incompatible with the process and/or product being evaluated, or that the sensitivity and/or specificity of the system is not what was originally anticipated. Therefore, careful planning and fact finding during the due diligence phase is critical to a successful RMM validation and implementation program.

The Validation Strategy

In order to design a holistic approach to RMM validation, it is necessary to develop a comprehensive strategy that includes qualifying not only the RMM instrumentation but the analytical method as well. The validation plan can be comprised of a number of process steps and these are outlined in the following sections.

Risk Assessment

Quality risk management (QRM) is an important part of science-based decision making which is essential for the quality management of pharmaceutical manufacturing. The ICH Q9 guideline, Quality Risk Management [1], defines QRM as a systematic process for the assessment, control, communication and review of risk to the quality of drug product across the product lifecycle. Similarly, the FDA Final Report for Pharmaceutical cGMPs for the 21st Century - A Risk-Based Approach [2], states that using a scientific framework to find ways of mitigating risk while facilitating continuous improvement and innovation in pharmaceutical manufacturing is a key public health objective, and that a new risk-based pharmaceutical quality assessment system will encourage the implementation of new technologies, including RMMs, to facilitate continuous manufacturing improvements via implementation of an effective quality system.

A risk assessment should be performed prior to the start of any RMM validation activities. Identified risks will vary depending on the RMM technology and the RMM supplier, the method the RMM is intended to replace, the product or sample(s) for evaluation, whether the new measurements are qualitative or quantitative and if the resulting data are significantly different from the existing method, method variability, method robustness, pharmacopeial equivalence, regulatory acceptance, and other attributes. Tools such as Failure Modes and Effects Analysis (FMEA) or Hazard Analysis and Critical Control Points (HACCP) may be utilized in assessing the potential risks when implementing the RMM.

Validation Master Plan (VMP)

A VMP should be followed which will provide the roadmap for all of the activities that will be required to demonstrate that the RMM is validated and suitable for its intended use. The VMP should include the overall project deliverables, the organizations or individuals that are responsible for each phase of test execution, review and approval, and the documentation required to satisfy the expectations of the validation strategy.

User Requirements Specifications (URS)

When choosing a RMM, the end-user must first establish the basic expectations that the system must meet. For example, the system may have to detect and enumerate bacteria, fungi and spores, have a sensitivity level of a single viable cell, process at least 80 samples within an 8-hour shift, and show (at least) equivalent results to the current method. From here, the user can develop specific requirements for the entire RMM system, including the equipment and the analytical method, which will demonstrate that the system performs as expected. The document that describes the functions and characteristics that the RMM system must be capable of performing is called the URS. The requirements specified in the URS can also form the basis for all of the validation testing requirements, test protocols and acceptance criteria.

Design Qualification (DQ)

Design Qualification (DQ) is documented verification that the proposed design of the equipment or system is suitable for the intended purpose. Because most RMMs are commercial off-the-shelf systems (COTS), DQ is accomplished by verifying that the supplier's design specifications meet the design requirements as specified in the URS. This activity can be completed prior to purchasing the RMM system or can be incorporated into the formal VMP.

Supplier Assessment/Audit

The URS should include requirements that the RMM supplier should meet. An example is that the supplier has an appropriate quality system for designing, manufacturing, testing and release of equipment, software, reagents and consumables throughout the RMM

life cycle. Other requirements may include the provision of technical documentation, training, troubleshooting, calibration and/or field service support. An assessment of whether the supplier can meet these requirements should be conducted, either through a review of relevant documentation provided by the supplier and/or an audit at the supplier's manufacturing and design/development facilities.

Functional Design Specifications (FDS)

The FDS is the document that describes all of the functions and requirements for the RMM system and what will be tested to ensure that the system performs as specified in the URS. The FDS can be quite extensive, covering system functionality, configuration, input/outputs, environment, utilities, architecture, interfaces, data and security. Additionally, the FDS will point to specific test scripts where each requirement will be tested and verified against pre-established acceptance criteria. These test scripts are normally contained within the Installation, Operational and Performance Qualification protocols.

Requirements Traceability Matrix (RTM)

The RTM is a document that provides traceability that all the requirements listed in the FDS have been verified and/or tested. Think of the RTM as a checklist of the validation process. The document identifies the test script or protocol where a function or requirement will be tested, such as the Installation, Operational and Performance Qualification (IQ, OQ and PQ, respectively) protocols. The RTM also specifies which SOPs and other documentation that needs to be in place in order to satisfy the criteria for meeting a specific function or requirement. The RTM is a living document during the execution of the validation test scripts or protocols.

Training and SOPs

Training with the RMM supplier and the proper qualification of analysts are required for the effective execution of the testing protocols and are critical to the success of the overall validation plan. Training may be scheduled during initial proof-of-concept or feasibility testing, either in-house or at the supplier's facility. SOPs that facilitate the proper execution of the RMM instrumentation, as well as those that are required to be in place as specified in the URS and FDS should be written and approved prior to the execution of the validation plan.

The Test Plan

The Test Plan identifies the formal testing strategy, resources, roles and responsibilities, test procedures, test deviation handling, and required deliverables for the validation program. This is the document that provides very specific test scripts and protocols, and their associated acceptance criteria, which will test and verify each function and requirement as specified in the URS and FDS. The RTM is the checklist that documents that each of the functions and requirements have been tested and/or verified. The manner in which the functions and requirements will be tested are specified in the IQ, OQ and PQ protocols.

Installation Qualification (IQ)

The IQ establishes that the equipment is received as designed and specified, that it is properly and safely installed with the correct utilities in the selected environment, and that the environment is suitable for the operation and use of the equipment. Basically, the IQ verifies that the equipment was received and meets the design specifications for the equipment that was ordered. The IQ can be carried out by the RMM supplier or by the end-user.

Operational Qualification (OQ)

The OQ provides documented verification that the equipment, as installed in the selected environment, performs effectively and reproducibly as intended throughout the anticipated or representative operational ranges, defined limits and tolerances. During this phase of the validation test plan, the end-user may confirm their previous proof-of-concept testing and/or the RMM supplier's supporting data. The OQ is also the focal point for the majority of the computer system, software and security validation activities, as well as demonstrating that the microbiological method is appropriate for its intended application. The latter is usually accomplished using standardized microorganism cultures and test samples/product matrices, while demonstrating that pharmacopoeia validation criteria are met.

Computer system validation encompasses both hardware and software functionality and security, and demonstrates that these components of the RMM system operate accurately and reliably. Depending on the complexity of the RMM technology and the end-user's company policies, CSV can be quite extensive.

Functional testing for the microbiological components of the RMM can be demonstrated by following the validation recommendations provided by the Parenteral Drug Association (PDA), the United States Pharmacopoeia (USP) and the European Pharmacopoeia (Ph. Eur.).

The PDA provided the first true guidance on RMMs, Technical Report #33, Evaluation, Validation and Implementation of New Microbiological Testing Methods [3]. Published in 2000, this document provides information on validation protocol design, testing and acceptance criteria, and installation, operational, and performance qualification strategies. Shortly thereafter, both the USP and the Ph. Eur. published informational chapters on the same subject.

USP informational chapter <1223>, Validation of Alternative Microbiological Methods [4], provides guidance for the validation of methods for use as alternatives to official compendial microbiological methods. The chapter incorporates the analytical concepts from USP <1225>, Validation of Compendial Methods, and relates these to alternative quantitative and qualitative microbiological systems. Although there is no guidance on qualifying new microbial identification systems, the USP has recently published a separate draft informational chapter on this topic.

Ph. Eur. chapter 5.1.6, Alternative Methods for Control of Microbiological Quality [5], describes alternative methods for the control of microbiological quality. A discussion of qualitative, quantitative and identification tests and guidance for using validation criteria are provided.

A test protocol is designed to evaluate the RMM against a variety of validation criteria that are specified in the PDA, USP and Ph. Eur. guidance documents, and the resulting data is compared against acceptance criteria specific for the validation criteria being assessed. Standardized microorganism cultures are used, and the concentration, number of replicates and type of microorganisms (e.g., bacteria, fungi, stressed, dead, mixed cultures, inoculated within a test sample) will be dependent on each validation criteria protocol and their acceptance criteria requirements. Additionally, many of the test protocols will require the use of an appropriate statistical model to determine if the resulting data meets the acceptance criteria as specified.

Performance Qualification (PQ)

The PQ provides confirmation that the entire RMM system performs as it is intended to by using actual product and/or test samples in order to demonstrate equivalence to the existing or reference method. This may include running the RMM in parallel with the current method for a specified period of time or number of batches or samples. Test samples should be identified, when appropriate, that are expected to contain microorganisms and some samples that are not, in order to test the suitability of the RMM. At least three independent tests using at least three different lots/batches of the test sample should be assessed. The actual number of batches, replicates, sample size and/or duration of testing will be defined as a function of the application.

A statistical analysis of the resulting data should be conducted in order to demonstrate equivalency between the two methods. There is the possibility that the RMM may recover a higher number of microorganisms as some technologies are not dependant on the growth of microorganisms, and cells that are physiologically stressed and/or damaged may not be detected on conventional, growth-based media.

Furthermore, the RMM may report the detection of viable microorganisms as a completely different measurement than colony forming units (CFUs), such as fluorescent units, relative light units or genetic copy number. In this case, a strategy should be developed for determining the correlation of the new data with the existing method's data, and whether there may be an impact to existing acceptance levels or in-process/product specifications. This strategy should be incorporated into the validation plan, and if necessary, within specific testing protocols.

Finally, when conducting equivalency testing using test samples that will not normally contain microorganisms, as would be expected during sterility testing, other strategies for demonstrating equivalency may need to be developed. For example, standardized cultures may be diluted to a theoretical level of less than 1 viable cell. The resulting suspension is then inoculated into the test material such that a proportion of the inoculated samples will contain a microorganism and the remaining proportion will not. The two methods may be determined to be equivalent if the proportion of positive to negative results is not statistically different.

Summary

Once the validation plan has been executed and approved, the rapid method may be implemented for routine use. Each type of rapid method and its intended application will, most likely, require a separate validation strategy; therefore, it is important to carefully consider all of the activities that will be required to demonstrate that the RMM instrumentation and the method is appropriately qualified and suitable for its intended use. A more in-depth review of RMM validation strategies may be found at http://rapidmicromethods.com, a new website dedicated to the advancement and implementation of rapid microbiological methods that is due to launch in May 2010. **APR**

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