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Validating your RMM technology

Understanding the process and developing your approach

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If you have kept up with prior spotlights, you have gained a great understanding of the RMM solutions that are available and the various benefits of each approach. The next logical question may now be, "what does it take to validate these solutions". Much like the different types of RMM approaches, the validation process can vary. Validation of the RMM solution requires understanding both internal and external requirements to appropriately validate the RMM solution. In addition, time and resource budgeting for validation is an important consideration. First, let's look at the requirements.

Sources of information and guidance:

Both the United States and European Pharmacopoeia's offer guidance regarding validation of microbiological methods. A recent USP presentation highlights some of the chapters that deal with validation of rapid methods.

- US Pharmacopoeia Chapter <1223>, "Validation of Alternative Microbiological Methods"
- European Pharmacopoeia Chapter 5.1.6 section 3.1 Types of Microbiological Tests states "For example, a sterility test by membrane filtration may be performed according to the pharmacopoeial procedure up to the point of combining the processed filter with the recovery media, and after that the presence of viable cells might then be demonstrated by use of some of the available (RMM) methods. Validation of this application would, therefore, require validation of the recovery system employed rather than the entire test."
- PDA Journal of Pharmaceutical Science and Technology Technical Report 33, "Evaluation, Validation, and Implementation of New Microbiological Testing Methods". This report highlights details around validation of new test methods, stating that, "The two critical components of any definition of validation are appropriateness of a specific product or process (it does what it purports to do) and reproducibility (it continues to perform)."

If the methods used in the QC/QA lab at the production facility are explicitly defined in the product license, expect additional steps that include a formal application to change the license to include the RMM method. Based on the risk of the change to the product quality, the route of license change may be as simple as an annual report or more complex by a CBE 30 or CBE 60 (Changes Be Effected), or for a critical change a prior approve supplement (PAS) may be required. The FDA has an initiative called the comparability protocol that facilitates faster license changes. The use of this route effectively allows a CBE 0 to be used, helping to streamline the process.

Steps in the Validation Process

When validating your RMM technology, there are key areas of qualification to be addressed:

* Installation qualification (IQ) – During the IQ phase of validation, the device is installed and verified for details such as the following:
o That the contents of delivery for the device match the order
o That the utilities are correct for the device

o Any documentation relative to the system is present (i.e. user manuals)
o Any documentation related the device, (i.e software, printers, etc) is present.

* Operational qualification (OQ) – The OQ phase of validation involves performance of the following steps:
o Ensuring that specific features work with in specific limits (i.e. temperature mapping for incubators when applicable)
o Verifying performance of specific devices, such as a barcode scanner
o Confirming the performance of any software required for the device in terms of controlling incubation, time and temperature, for example, and 21CRF11 compliance.

* Performance qualification (PQ) – During the PQ step, the following key activities take place:
o Time to results are determined for the specific organisms
o The accuracy of any software involved in colony counting is verified.
o Recovery of pharmcopial organisms is verified.

* Method suitability – Testing method suitability ensures the device works with the specific product of interest; this also includes equivalence testing to ensure that the new rapid method is equivalent to the current method. Method suitability involves steps such as the following:
o Verification that product of interest has no inhibitory or adverse affect on the technology
o Testing of equivalence against the control method (usually the current in-house method)

Rapid micro methods vendors will generally have validation packages that include templates of the documents required during each step to help streamline the qualification process. Approaching the validation process can seem daunting. But the best strategy is to break the validation into steps, and where possible engage your vendor, who will have more experience in validating their system.

An Example:

IQ and OQ

For biopharmaceutical companies that are navigating the validation process, the first step is the determination of the guidelines from which to base the validation. Typically, our customers look to our team to perform the IQ and OQ steps of the process. In the case of Growth Direct, the OQ step required that Growth Direct was validated according to the requirements of USP <1058>.

PQ and Method Suitability

For the Performance Qualification and Method Suitability steps, analytical equipment qualification and the automation of enumeration are validated against guidelines in USP <16> and USP <1227>. To comply with these chapters, assessments of accuracy and precision were tested. Repeat testing of 6 to 10 replicate organisms of interest are analyzed using the Growth Direct and Control methods. Results are statistically compared for equivalence.

Method Suitability requires a panel of products to be tested. Those products were reviewed and divided into “families” of product types. Example products from each “family” were tested to minimize the testing performed. This strategy created a 20% reduction in the amount of required testing. Method suitability tests two main parameters:

- Testing product matrix to verify that there are no inherent characteristics that will affect the detection process (in our case imaging) e.g. high particulate count or fluorescent background
- Testing spike and recovery according to USP Chapter <61>, USP Chapter <1227> and EP Chapter 2.6.12. as per the traditional culture test with three lots of product and using <100 CFU of the Pharmacopoeial specified micro organisms and any environmental isolates that may be relevant.

- In both cases, a suitable number of replicates were tested to determine any potential impact. Method suitability testing included the analysis of product with and without bacterial inoculation and verification that the device enumerated the colonies accurately with no background issues.

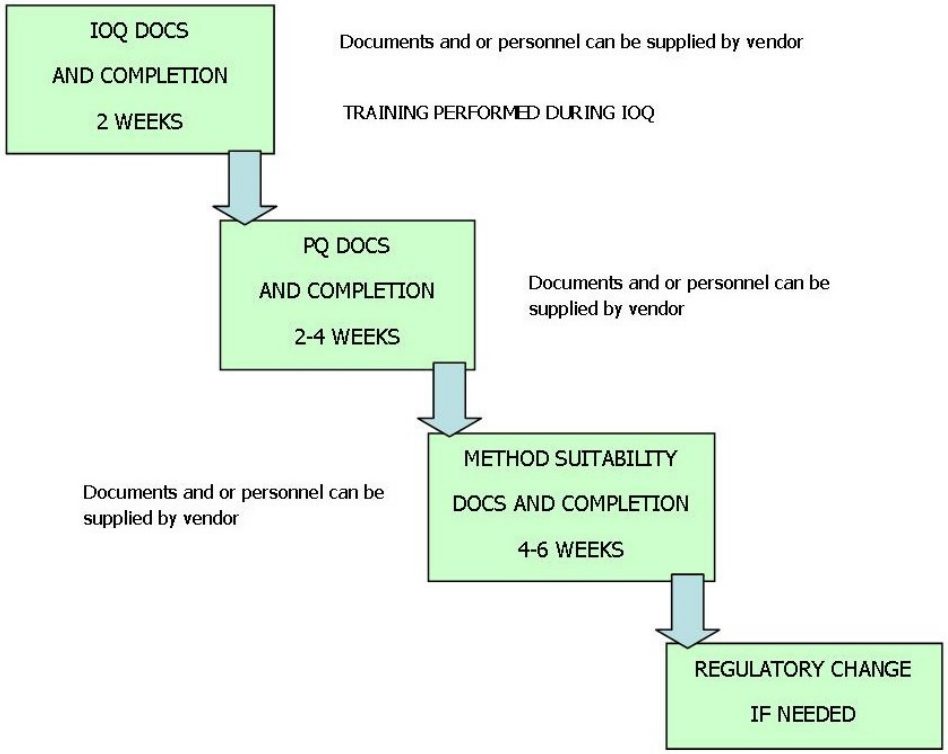
Standardization and repeatability are key

One customer who is in their validation process noted the importance of standardization of processes to successful and streamlined validation. For them, the following guidelines were of key importance:

- Create a center of excellence for RMM operations
- Develop validation protocols centrally
- Create a knowledge and technology transfer process from one site to the next
- Take advantage of vendor expertise
- Standardize as much as possible
- When submitting validation documents, Include any literature on the technology in your dossier – including any peer reviewed documents, other customer testimonials, etc.

The chart of the validation process illustrated below shows the minimal times to successfully complete validation in an optimal environment.

Example Validation and Qualification of RMM



Conclusion

Rapid micro methods offer significant benefits to the micro QC lab and Production. Selecting the appropriate solution and working closely with your RMM vendor helps streamline the installation and validation process.

References

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