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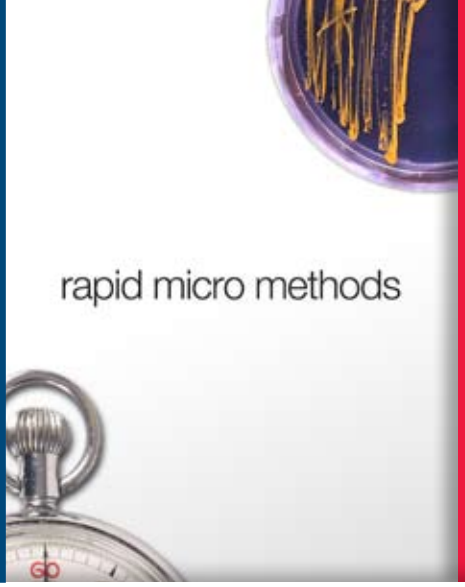

It's Time to Get Rapid!

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When PDA *Technical Report No. 33 Evaluation, Validation and Implementation of New Microbiological Testing Methods* was first published in 2000, it was assumed that the pharmaceutical and biopharmaceutical industry would recognize and accept the benefits of implementing rapid microbiological methods (RMM) as an alternative to conventional, growth-based methods and to utilize the technical report as a roadmap for qualification and implementation strategies. Although a number of firms have implemented RMM platforms for a variety of in-process and finished product release tests, the mass exodus from conventional methods has not occurred as quickly as originally anticipated. It is important to fully understand the reasons for the industry's hesitancy because it has been demonstrated that RMMs can contribute to the continuous improvement and capability of pharmaceutical processes, encourage manufacturing efficiencies and agility, and enhance the quality of drug products throughout their life cycle. A recent survey suggests that we continue to express apprehension about the cost, validation and regulatory acceptance for implementing RMMs.[1] If we are to effectively move away from 19th century microbiology methods and embrace currently-available 21st century technologies, it is necessary to explore each of these concerns and provide clarity around what is perception, what is reality and what might be just operating with our eyes wide shut.

Is There Really An Issue With Cost?

There are obvious costs involved with the purchase, qualification and implementation of RMMs. Depending on the capital expense, the manner in which the system will be employed and the process required to adequately validate the system for its intended use, the cost associated with implementing a RMM can be significant. However, it is imperative that the potential end-user comprehends the bigger picture; namely, the costs associated with the existing method, the costs associated with the initial RMM investment and the long-term financial benefits or savings that the RMM may provide. A number of economic models are available that can easily calculate the return on investment, payback period and net present value when implementing a RMM, and I recently reported significant cost savings over a five year period when implementing an automated environmental monitoring (EM) RMM the (BioVigilant® IMD-A™) as an alternative to manual, active air sampling.[2] In this example, the elimination of sampling and testing resources, lab space and lab equipment, and the ability to immediately react to an EM excursion instead of three to five days after the event provided sufficient economic justification to

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validate and implement the IMD-A for routine use. Therefore, conducting a comprehensive financial analysis and linking this information to other business, technical and quality benefits that the RMM may afford should permit a firm to make an appropriate decision on whether or not to proceed with an implementation plan.

Is There A Guidance On Validating A RMM?

Absolutely. In addition to TR-33, the United States and European Pharmacopoeias both have informational chapters on this subject. USP <1223> *Validation of Alternative Microbiological Methods,* and EP 5.1.6 *Alternative Methods for Control of Microbiological Quality* provide recommendations on the use of RMM validation criteria, such as accuracy, precision, specificity, limit of detection, limit of quantification, linearity, range, robustness, ruggedness and equivalence. Both of these documents show similarity to the current TR-33; however, slight differences do exist, which may make it somewhat difficult to design a validation plan that will satisfy the expectations and acceptance criteria for all three. Furthermore, there is a need to provide greater detail on the practical side of the validation process, such as the selection of an appropriate statistical model for each of the validation criteria, what to do in the event a RMM provides greater counts than the conventional method, evaluating false positives, false negatives and system noise, and the potential impact of stressed, injured and/or viable but non-culturable organisms. For these and other reasons, TR-33 is currently undergoing a substantial revision process that is due to be completed by the end of this year, and I will be presenting an overview of these changes during the PDA Annual Meeting in Las Vegas. Although the revised TR-33 will provide a more comprehensive guidance document for RMM validation and implementation strategies in the future, the industry has successfully utilized the current TR-33, USP and EP informational chapters for the qualification of many RMM systems for use in both the United States and in Europe.

Do Regulatory Authorities Encourage The Use Of RMMs And Are There Policies In Place That Make It Easy To Get A RMM Approved?

The answer to both of these questions is "yes"; however, RMM approvals may be *easier* than others depending on the regulatory agency involved, the RMM intended use, and whether or not an existing microbiology method (one that will be replaced by the RMM) is included in a new drug application or marketing authorization. Let's explore each in more detail. There are several regulatory guidance documents that encourage the use of new microbiological

According to some industry experts, the era of the agar plate is coming to an end and the time for rapid methods is now.

Photo courtesy of BioVigilant Systems, Inc.

technologies, including RMMs. The U.S. FDA *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing* states that other suitable microbiological tests (e.g., rapid methods) can be considered for EM, in-process control testing and finished product release testing after it has been demonstrated that these new methods are equivalent or better than conventional methods (e.g., USP). Additionally, the FDA Process Analytical Technology (PAT) initiative describes a regulatory framework that will encourage the voluntary development and implementation of innovative approaches in pharmaceutical development, manufacturing, and quality assurance. Many new technologies are available that provide information on physical, chemical, and *microbiological* characteristics of materials to improve process understanding and to measure, control and/or predict quality and performance. Furthermore, the FDA Center for Biologics Evaluation and Research has recently provided a draft Guidance for Industry entitled *Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products.* The guidance is specifically focused on growth-based methods for cellular products, and a validation approach similar to what is contained in the guidance was used by Genzyme Biosurgery to gain approval to use the bioMerieux BacT/ALERT, a growth-based RMM, for the sterility testing of cell-based products. Next, **Brenda Uratani**, PhD, Consumer Safety Officer, U.S. FDA, recently described the benefits of using a RMM during *PDA's 2nd Annual Global Conference on Pharmaceutical Microbiology*. She spoke about automating the testing process, electronic capture of test data and information creation, the ability to initiate investigations earlier as compared with conventional methods, the reduction of risk associated with microbial contamination and the use of the data as a continuum for process improvement. Finally, both the FDA and EMEA have provided a number of regulatory approvals for the use of RMMs as alternatives to conventional microbiological testing. For example, GlaxoSmithKline received FDA-approval to use the Pallchek ATP bioluminescence system for the rapid release of a non-sterile, prescription nasal spray, and more recently, Alcon Laboratories received FDA-approval for a rapid sterility test using the AES-Chemunex ScanRDI.

Regulatory agencies will generally accept a change in a manufacturing or testing process if the change has been proven to be equivalent to or better than the system currently in place. However, the acceptance of RMMs by regulatory authorities throughout the world has been somewhat varied, and it is this variability that may be a concern when considering an implementation and regulatory strategy. For example, a single facility may manufacture a product for distribution to a number of different countries and would therefore be regulated by an equal number of independent regulatory authorities. With global regulatory harmonization unlikely in the near future, the ability to understand the requirements of multiple regulatory authorities may be necessary when considering RMMs. For the purpose of this discussion, I will primarily focus on the current policies in the U.S. and Europe.

Within the United States, PDA TR-33 and USP <1223> can serve as a jumping off point for discussions with the FDA on the validation and implementation of a RMM. There are a number of options for qualifying a RMM that will be used to support the manufacture of FDA-regulated drug product. If the RMM will be used with a new product, a firm may include the RMM in a new drug application or an abbreviated new drug application. If the RMM will be used with an existing product, and the RMM will replace a microbiology method that has been included in the product's original regulatory submission, then it may be necessary to file a post-approval change or prior-approval supplement in the relevant Chemistry, Manufacturing and Controls (CMC) sections for that product. Once a RMM has been approved, either in an NDA, ANDA or a prior-approval supplement, subsequent product filings may include the RMM in an Annual Product Report. Another option is to file a comparability protocol (CP) and manage the method change through the FDA PAT initiative.

A CP is a well-defined, detailed, written plan (and prior-approval supplement) for assessing the effect of specific CMC changes in the identity, strength, quality, purity and potency of a specific drug product as these factors relate to the safety and effectiveness of the product. The CP describes the changes that are covered under the protocol and specifies the tests and studies that will be performed, including the analytical procedures that will be used, and acceptance criteria that will be achieved to demonstrate that specified CMC changes do not adversely affect the product. Furthermore, the CP can be particularly useful for changes of a repetitive nature, such as the use of a RMM for multiple products or processes. More importantly, the use of a CP simplifies the process of reporting the change, especially when the approved CP covers subsequent CMC changes for multiple products and/or multiple microbiology applications. Once the CP is approved, the experiments are performed, and if they meet the acceptance criteria provided in the CP, a

special report [21 CFR 314.81(b)(3)(ii)] to the relevant application is submitted. The special report references the approved CP and includes a brief description of the RMM and its use, confirmation that the acceptance criteria have been met and the date of implementation. The special report is a very brief document, as small as one page, because there is no need to provide any data in the report. Under this strategy, any future CMC changes covered under the approved CP can be made without the need for additional approvals, and a reduced reporting category can be realized, such as a changes being effected (CBE)-30 or CBE-0. It should also be noted that CPs have been successfully used by a number of firms to implement RMMs for FDA regulated products.

For many RMMs, the FDA is now encouraging changes to be managed under the PAT model, especially if the intended change is for an in-process test, such as bioburden and purified water testing and EM. In this case, the PAT submission will be assigned to a PAT Review, Inspection and OPS Policy Development Team (PATRIOT) consisting of CMC reviewers, compliance officers and investigators. The PAT application can include the use of a CP and pre- and/or post-approval inspections. Because the most appropriate regulatory strategy (PAT, CP, prior-approval supplement, etc.) will depend on the microbiology method change, the manner in which the method will be used, and the product(s) that will be affected, it is highly recommended to discuss the proposed change with the FDA early in the implementation process. This is especially true for RMM changes that will impact in-process microbiology methods that are not included in an NDA or ANDA, because the change may actually be managed through a firm's internal change control program instead of a formal regulatory process. Finally, the FDA expects that higher counts will be recovered when using RMM technologies that are more sensitive than conventional methods.[3] In this instance, any potential changes to existing microbial specifications should be discussed when developing the RMM regulatory strategy.

Lasers are used in the real-time detection of airborne microorganisms

Photo courtesy of BioVigilant Systems, Inc.

Like the USP chapter <1223>, EP 5.1.6 can provide a starting point for discussions with European regulators in developing an appropriate strategy for the validation of RMMs. Although specific issues can be expected from individual member states during the registration process, the mutual recognition process does help to reduce questions and ultimately saves time and effort on the part of the applicant. However, the current European regulatory environment (for gaining RMM approval) may not be as straightforward as in the United States. Although individual member states have approved RMMs for routine use, many of the tools provided by the FDA do not exist within the EMEA. For example, there is no equivalent to the comparability protocol in Europe, and for those RMMs intended to replace existing microbiology methods that have been incorporated into marketing authorizations, the filing of multiple type variations may be required for each product, instead of being managed under a single CP. On the other hand, RMMs that are intended to replace existing methods that are not part of a regulatory dossier may manage the change internally and without the need to submit a formal regulatory submission. In either case, greater emphasis is given in Europe to equivalence testing between a RMM and the conventional test it is intended to replace. This contrasts to the situation in the United States where equivalence is not seen as such a priority due to the very different natures of new and conventional methodologies. Finally, the European PAT initiative has been taking shape over the last few years, but

it still isn't as far along as the United States with respect to RMMs. Although we wait for future direction from the EMEA on how RMM PAT submissions will be handled in the future, it is obvious that the European authorities are receptive to new technologies and are open to dialogue with firms interested in RMM implementation. As a final note, discussions were held with the EMEA Quality Working Party and the ad hoc GMP inspector's group with respect to the use of RMMs for the assessment of purified water. The two groups acknowledged EP 5.1.6 and the acceptability of rapid microbial methods to replace the standard pharmacopoeial methods provided appropriate validation is performed. It was then suggested that the introduction of such methods might require specific review to ensure that the appropriate validation steps (in EP 5.1.6) have been followed and that the water continues to meet the Ph. Eur. specifications. Since, in the case of water, the validation will not be product specific, it was further suggested that a company could request the supervisory authority to carry out a specific site inspection, and the performance of such an inspection would be at the discretion of the supervisory authority and could involve a pharmaceutical assessor where necessary. Since it is expected that the water will continue to meet Ph. Eur. specification, if tested, no change to dossier requirements (variations) would be involved and therefore no regulatory impact on individual products would normally be anticipated. This would, however, depend on the level of detail in the original dossiers concerned.

Whether a firm plans on satisfying the expectations of the FDA, EMEA or another regulatory authority, it is very important to discuss the RMM qualification and implementation plans with the relevant agency early in the design phase to ensure that the best strategy is agreed upon.

What Does The Future Of Rapid Methods Look Like?

For sterile products, I envision using RMMs to support the parametric release of aseptically-filled product. That's right, parametric release. Let's put this idea into perspective.

The EMEA *Note for Guidance on Parametric Release* (CPMP/QWP/3015/99) defines parametric release as a system of release that gives assurance that the product is of the intended quality based on the information collected during the manufacturing process and on the compliance with specific GMP requirements related to parametric release. Consequently, parametric release is used as an operational alternative to routine release testing of certain, specific parameters. For terminally sterilized product, this means that a batch is released based on process data rather than on a finished product sterility test. In November 2008, the EMEA published a concept paper on the revision of the *Guideline on Parametric Release.* The problem statement is that the current guidance for parametric release does not reflect the recent regulatory development on PAT, Quality by Design and real time release. This is where the true potential for RMMs comes into play. If we are able to generate real-time and continuous microbiological monitoring data during aseptic processing, while operating in an environment that eliminates human-borne contamination, such as an isolator, we may be able to justify the elimination of the end-product sterility test because we will demonstrate (during manufacturing) that the finished product is of the intended quality with respect to microbiological control. We would, therefore, need to put in place continuous and real-time technologies for the analysis of raw materials (e.g., purified water), pre- and post-filtration bioburden and EM. Today, there exists a RMM technology that can deliver at least one of these deliverables for EM. The BioVigilant® IMD-A™ has the ability to continuously monitor manufacturing environments (i.e., conventional cleanrooms, isolators and RABS) for both viable and non-viable particles and reports the data in real-time. Amgen Quality VP **Martin Van Trieste** recently commented that the BioVigilant system represents a paradigm shift in the way we can perform EM.[4] He stated that rather than having to be reactive, the system allows firms to "look ahead of time and say, 'is there anything there that I should be concerned about and do something about before I put my product at risk?'" Additional insights into the BioVigilant® IMD-A™ will be presented during the *2009 PDA Annual Meeting* in Las Vegas, where I will share a case study on the use of the technology for real-time EM in manufacturing isolators. Furthermore, two papers detailing these studies will be published in the PDA Journal mid-year.

In closing, the implementation of RMMs represents significant progress toward the acceptance of microbiological PAT solutions for the industry, and is directly aligned with the expectations for pharmaceutical manufacturing, quality and operational excellence in the 21st century. It is time for the industry to move forward and embrace the future of microbiological methods. It really is time to get rapid!

References

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Cover art:
According to some industry experts, the time for implementing Rapid Microbiological Methods is now.