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Article 4



The implementation of rapid microbiological methods

This is the fourth in a series of articles on rapid microbiological methods that will appear in European Pharmaceutical Review during 2010. Believe it or not, today's regulatory authorities encourage the use of rapid microbiological methods (RMMs), and when applicable, they have put policies in place that provide guidance on how to get a RMM approved. Because there are different regulatory perspectives on RMM implementation, a company should understand what each regulatory body expects with regard to validation, submission and implementation strategies. In my last article, I discussed a number of RMM implementation perspectives from the U.S. Food and Drug Administration (FDA). In this article, I will focus on the European Medicines Agency (EMA) and their expectations on the introduction of new RMM technologies.

Like their U.S. counterparts, European regulators have been supporting the industry to validate and implement RMM and PAT technologies. For example, Paul Hargreaves (Technical Manager, U.K. Medicines and Healthcare Products Regulatory Agency; MHRA) has viewed the implementation of alternative microbiology methods as a positive step in improving the quality of medicines and patient safety, and has actively encouraged the industry to implement these technologies for many years¹. Additionally, in order to support PAT activities in the European Union (EU), an EMA PAT team was created that includes the Quality Working Party and the ad hoc GMP/GDP Inspectors Working Group. The aim of this team is to review the implications of PAT and to ensure that the European regulatory framework and the authorities are prepared for and adequately equipped to conduct

thorough and effective evaluations of PAT-based submissions. The EMA PAT team believes that the current regulatory framework in Europe is open to the implementation of PAT in marketing authorisation applications, especially when the application includes Quality by Design (QbD) strategies. In addition, the ICH Guideline on Pharmaceutical Development (ICH Q8)², now adopted by EU, also includes provisions on the use of PAT applications.

Unfortunately, only a small number of RMM regulatory applications have been submitted in the EU, and regulators have expressed their disappointment in the industry's hesitancy in embracing the change from conventional methods to alternative methods. One reason for this apparent lack of willingness to move microbiology technology forward has been the industry's perception that the current European

regulatory framework actually hinders, instead of encourages, the implementation of RMMs. For example, many end-users consider the European regulatory environment for submissions as being more complicated and not as straightforward as the procedures they have used for RMM approvals in the U.S. Although individual member states have approved RMMs for routine use, many of the tools provided by the FDA do not exist within the EMA. Next, there is no equivalent to the comparability protocol in Europe, and companies have had no formal process for submitting a RMM validation strategy for review and approval prior to the initiation of the actual testing plan. For some companies, it has taken almost 18 months for their RMM validation dossier to be reviewed and commented on by numerous member states, thereby extending the time for RMM implementation. Furthermore, for those RMMs intended to replace existing microbiology methods that have been incorporated into marketing authorisations, the filing of multiple type variations has been required for each product and facility, instead of being managed under a single comparability protocol, which is the strategy that many companies have used in the U.S. This process is both time-consuming and costly. Therefore, in order to encourage the industry to implement RMMs within the EU, it is critical that the

regulatory environment change in order to relieve the regulatory burdens associated with RMM validation strategies, and for the EMA to move towards a simpler, clearer and more flexible framework with regard to type variations. Fortunately, significant changes have very recently occurred which paved the way for a friendlier and simpler strategy for RMM implementation within Europe.

Revisions to type variations

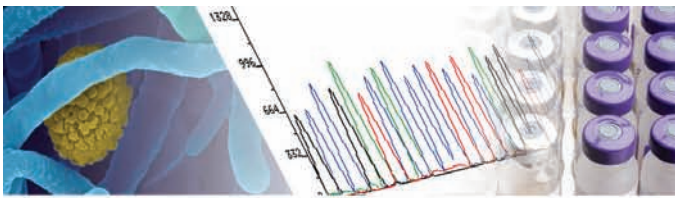
On 1 January 2010, new revisions to variations regulation 1234/2008 went into effect and apply to variations to a marketing authorisation granted in a Mutual Recognition / Decentralised Procedure and to Community or Centralised authorisations⁵. The new variations regulation introduces a number of features such as annual reporting for minor type IA changes, type IB by default and implementing new procedures such as 'work-sharing' and 'grouping of variations' aiming to reduce the workload for both competent authorities and applicants. With the review of the variations regulations (new variations regulation 1234/2008) and the release of Directive 2009/53/EC for changing the legal basis of the variations regulation, the way towards the last major change has been cleared: all authorised medicinal products, including those authorised at the purely national level, will now be subject to the same criteria for the evaluation, approval and administrative handling of changes, regardless of the procedure under which those medicines have been initially authorised. These changes were previously outlined in the 2007 public consultation paper, *'Better Regulation of Pharmaceuticals: Towards a simpler, clearer and more flexible framework on variations'*. More importantly, the changes will have a significant impact on the way RMMs will be implemented in Europe and this was the focus of a full-day meeting hosted by the Parenteral Drug Association (PDA) on 21 September 2009 in Frankfurt, Germany. An overview of the major discussion points during this meeting is provided below.

PDA forum on implementing RMMs in Europe

European regulators agreed to dedicate a discussion forum to practical questions about the implementation of RMMs in Europe, as the process appeared to not be well understood by the pharmaceutical industry. Specifically, it was perceived that:

- ◆ Implementing RMMs is a complex regulatory scenario
- ◆ It can become very costly, if variations to marketing authorisations are involved
- ◆ The time horizon to get approval for implementation might be unpredictable, especially if the product or products concerned possess heterogeneous marketing authorisations
- ◆ Discussions with regulators on scientific and practical questions seem not to be endorsed before a formal application is submitted, leaving the risk of missing aspects crucial to the authorities and related delays to the applicant

Three European regulators served as panellists during this meeting; they included Paul Hargreaves (MHRA inspector), Gustavo Marco (MHRA reviewer) and Riccardo Luigetti (EMA and PAT team member). Below are some of the topics that were discussed.



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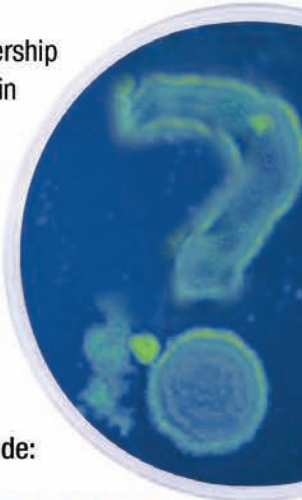
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Type variations

The revisions for type variations will provide clearer, simpler and more flexible options, reduced regulatory administrative burden, adaptation to ICH concepts and harmonisation across the national authorities. One of the most important changes relating to RMMs is that it will be possible to group variations under the same marketing authorisation such that they can all be assessed at the same time. Furthermore, it will be possible to combine the same variations or group of variations from different marketing authorisations and have all of these assessed at the same time under what is called a work sharing process (or a common assessment). This could be the case for a single RMM technology being used for multiple products. Finally, it is under discussion that there may be a possibility of having pre-authorised, post approval change management plans and protocols. Hopefully, we will hear more about these additional opportunities later in the year.

Scientific advice

There will be new opportunities for scientific dialog with regulators through the EMA Scientific Advice (SA) procedure. The SA procedure is used for scientific issues concerning quality, non-clinical and clinical aspects relating to the proposed future development of the medicinal product and focuses on general strategies. The SA procedure is also used during the early stages of product development but is not intended to offer a pre-review of data in support of a marketing authorisation application. The SA procedure applies to the entire EU; however, individual national authorities may require additional discussions in addition to the advice received under this procedure. The SA is not legally binding and can be contradicted once the application is under official review; however, you will receive an official document from the EMA SA working party.

Validation expectations

Ph. Eur. chapter 5.1.6¹ is the guidance that should be used when validating RMMs in Europe. The regulators are ready to evaluate the data from validation studies; however, there have been few RMM applications submitted and Riccardo Luigetti agrees that the existing process is moving slowly. He also stated that there is no prejudice or preclusion of introducing alternative microbiological methods. In fact, the EMA Quality Working Party (QWP) and the

ad hoc GMP inspector's group published guidance on using RMMs for pharmaceutical water including WFI⁵. The introduction of such methods might require specific review to ensure that the appropriate validation steps (in Ph. Eur. 5.1.6) have been followed and that the water continues to meet the Ph. Eur. specifications. Since it is expected that the water will continue to meet Ph. Eur. specification, if tested, no change to dossier requirements 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.

The primary validation should include a characterisation of the principle of detection using a panel of challenge microorganisms. A risk-benefit analysis should also be included which would address the limitations of both the RMM and the compendial method. The PQ demonstrates that the method has been validated for its intended use and this is performed using actual product. Additionally, the method must be comparable to test results characterised in a model system as evaluated by the vendor. Finally, the RMM must be shown to be at least equivalent to the compendial method. Furthermore, the specific characteristics of the microbial methods should be described, such as the use of specific equipment or method variability. It is also very important that the validation includes metabolically and physically injured organisms, starved cells, environmental monitoring isolates and spores, when applicable. Cells grown under ideal and stressed conditions can also be used to determine any differences between the RMM and the compendial methods.

Summary

This article provides a brief overview of EMA regulatory perspectives when validating and implementing RMMs. Because RMM qualification strategies can be influenced by the RMM technology, method or application, and/or the product or test sample, it is important to discuss your proposed plans with the relevant regulatory authority and/or local inspectorate in advance of finalising your testing approach. For a more in-depth review of the EMA's perspectives and validation expectations, you are encouraged to visit the Regulatory Information Page at <http://rapidmicromethods.com>, a new website dedicated to the advancement and implementation of rapid microbiological methods.

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Dr. Michael J. Miller is an internationally recognised microbiologist and subject matter expert in pharmaceutical microbiology and the design, validation and implementation of rapid microbiological methods. He is currently the President of Microbiology Consultants, LLC (<http://microbiologyconsultants.com>). In this role, he is responsible for providing scientific, quality, regulatory and business solutions for the pharmaceutical industry and suppliers of new microbiology technologies. Over the past 21 years, Dr. Miller has held numerous R&D, manufacturing, quality, consulting and business development leadership roles at Johnson & Johnson, Eli Lilly and Company, Bausch & Lomb, and Pharmaceutical Systems, Inc.

Dr. Miller has authored over 100 technical publications and presentations in the areas of rapid microbiological methods, PAT, ophthalmics, disinfection and sterilisation, is the editor of PDA's *Encyclopaedia of Rapid Microbiological Methods*, and is the owner of <http://rapidmicromethods.com>, a new website dedicated to the advancement of RMMs. He currently serves on a number of PDA's program and publication committees and advisory boards, and is co-chairing the revision of PDA Technical Report #33: *Evaluation, Validation and Implementation of New Microbiological Testing Methods*.

Dr. Miller holds a Ph.D. in Microbiology and Biochemistry from Georgia State University (GSU), a B.A. in Anthropology and Sociology from Hobart College, and is currently an adjunct professor at GSU. He was appointed the John Henry Hobart Fellow in Residence for Ethics and Social Justice, awarded PDA's Distinguished Service Award and was named Microbiologist of the Year by the Institute of Validation Technology (IVT).