Celsis
a charles river company

A Clear Path for Regulatory Approval of RMMs

A Celsis Rapid Detection Report

Presenting the current guidelines, regulatory expectations and available support for companies ready to adopt rapid microbiological methods (RMMs).

Reducing the manufacturing cycle time associated with traditional microbial test methods favorably impacts a company's production cycle times, quarantined in-process and safety stock inventories and working capital requirements; each of which generates significant financial benefit to operations. Further, RMMs allow for a higher level of quality assurance as manufacturers can identify and react to contamination events faster and therefore minimize the impact of such an event.

Rapid microbial methods have been gaining increasing industry acceptance since the early 1990s, when the personal care industry embraced RMMs. While slower to widely adopt these technologies, the pharmaceutical industry can benefit from the accumulated experience of the past decade. Recognizing the ongoing integration of RMMs into the microbiological testing environment, industry representatives and experts, along with regulatory agencies and RMM vendors, have helped define a clear pathway for the implementation of such technologies. And it could not have come at a better time—with today's economy putting pressure on businesses worldwide to reduce costs.

Smart science for smart business™

Clear Acceptance

Regulatory agencies around the world are increasingly familiar with rapid methods as submissions and approvals have become more commonplace. Global regulatory agencies are committed to accepting process changes or improvements if the proposed change has been shown to be equivalent to, or better than, the existing process. Global regulatory agencies support rapid methods. In fact, the Celsis rapid detection system has been included in approvals by every major regulatory agency, and approval for use of the Celsis method has never been denied.

> *"Alternative microbiological procedures, including automated methods, may be used, provided that their equivalence to the Pharmacopeial method has been demonstrated."*
>
> —Ph EUR 2.6.12, JP 4.05 I.1, USP <61>

As shown from the citation above, even the agencies governing the traditional microbial test methods openly express acceptance of alternate methods. The European, Japanese, and United States Pharmacopeias clearly state that an alternative method may be used.[1, 2, 3]

Demonstrating Equivalence

The *"equivalence to the Pharmacopeial method"* is demonstrated via the validation of the RMM. Like any other process improvement, the proposed method should undergo validation to confirm appropriateness and acceptability of the change. Celsis provides validation support and guidance to customers during the validation and implementation process to ensure a successful transition.

Validation Guidelines

Four primary guidance documents exist for the implementation and validation of an RMM:

- **PDA Technical Report 33** – Evaluation, Validation and Implementation of New Microbiological Testing Methods[4]
- **Ph EUR 5.1.6.** – Alternative Methods for Control of Microbiological Quality[1]
- **USP Chapter <1223>** – Validation of Alternative Microbiological Methods[3]
- **FDA CBER Draft Guidance Document** – Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products[5]

The PDA TR33 was created in 2000, via a collaboration between industry, RMM providers (including Celsis) and representatives of regulatory agencies. Both the USP and Ph EUR chapters followed shortly thereafter. All three guidelines are very similar with only minor differences between the documents.

In addition, in 2008, the U.S. FDA drafted its own guidance document regarding RMMs and sterility testing: **Draft Guidance for Industry: Validation of Growth-Based Rapid Microbiological Methods for Sterility Testing of Cellular and Gene Therapy Products.** While this guidance document focuses on a specific application (cellular and gene therapy products), allowances are made that "some of the principles of RMM validation discussed in this guidance might also be applicable to [other] products…" The article also recommends that a user "should discuss RMM validation for your product with the appropriate review office."

Commonalities

A review of the preceding guidelines reveals some commonalities in the testing recommended for the validation of a qualitative test. [Note that the Celsis method is an absence/presence (qualitative) assay.] Due to the nature of qualitative tests, fewer data parameters require addressing. The parameters are:

1. **Specificity:** The ability to detect a range of microorganisms.
2. **Limit of Detection:** Determination of the lowest amount of micro-organisms detectable.
3. **Ruggedness:** The resistance to influences of operational and environmental variables (random effects).
4. **Robustness:** The capacity to remain unaffected by small but deliberate (non-random) variations.
5. **Equivalence:** The ability of the two tests to return similar results.

It should be noted that the above parameters are common validation parameters and are not unique to RMM validations. Further, the guidelines also make provisions that RMM suppliers may provide vendor-generated data in lieu of or to supplement the user's validation data.

Regulatory Agency Expectations

When validating a Celsis rapid detection system, one should follow the usual validation parameters as outlined above, which include studies on specificity, limit of detection, ruggedness, robustness and equivalence. In addition, it is expected that the micro-organisms selected for the validation studies encompass the following categories:

- Gram negative
- Gram positive
- Yeast
- Mold
- Slow growing
- Fastidious for the RMM
- Isolates from environmental monitoring
- Isolates from starting materials
- Isolates from in-process and final product testing
- Microbes common for product type or application

For sterility applications, one should also include:

- Anaerobes
- Isolates from low-nutrient and high-stress environments
- Micro-organisms continually exposed to high nutrients

U.S. FDA Regulated Products

For products that are FDA regulated, the FDA has created the comparability protocol approach to streamline the submission and approval process. Used in conjunction with the validation process, a comparability protocol simply outlines the studies that will be performed and how the study results will be interpreted. Comparability protocols are provided for in the FDA guidance documents:

- *Comparability Protocols—Protein Drug Products and Biological Products; Chemistry, Manufacturing, and Controls Information*[5]
- *Comparability Protocols—Chemistry, Manufacturing, and Controls Information*[5]

Tools and Assistance

In addition to demonstrating a positive return on investment (ROI) for your company from implementing a rapid system, suppliers of RMMs should have a vested interest in successful adoption of the technology. As a partner in your RMM implementation, Celsis stands ready to accompany you on the pathway to validation and regulatory approval. Customers count on Celsis for:

- Global technical, scientific, regulatory and validation support
- Experienced regulatory compliance personnel on staff
- Accredited, CGMP laboratories for validation services
- A track record of multiple regulatory approvals dating back to 1997

Celsis also provides a number of tools to help customers streamline the approval process.

- The **Celsis Validation Guide** is a planning workbook, incorporating the information covered by the pharmacopoeias and the FDA and PDA guides. It includes specific information on validating the Celsis system. This Guide can readily serve as the basis of a company's validation package or comparability protocol.
- Two Celsis **Drug Master Files** (DMFs) have been accepted by the FDA. DMFs contain specific, confidential information and are shared only with the FDA, but can be referenced in regulatory submissions. The information aids the FDA during evaluation of regulatory applications and facilitates faster approval. They may save a company significant time in preparation too, as they summarize testing that has already been performed and therefore may not need to be repeated as part of the validation process.
- While the DMFs are proprietary documents that do not circulate, Celsis also makes a **Technical Report** available to customers. This report details many of the basic qualitative validation study elements that have been performed with Celsis systems over the years, including specificity, limit of detection, robustness and ruggedness. The report is available for inclusion with your validation or regulatory submission package as needed.

Pathway to Success

Wyeth Pharmaceuticals, in conjunction with Celsis, became the first pharmaceutical company to obtain regulatory approval to use a rapid microbial method for product release in 1997. Today, a majority of the top 10 pharmaceutical companies have implemented RMMs on at least one product. And all of them work with Celsis. The substantial financial benefits of rapid methods are giving pharmaceutical companies more reasons to take products down the road to regulatory approval. At the same time, regulatory bodies are busy paving the way for that pathway to become a super-highway. Implementing RMMs to drive the faster release of quality products is an achievable goal, and it can deliver significant, bottom-line benefits to your company.

References

1. European Pharmacopoeia (Ph EUR), edition 6.3, 1/2009, Chapters 2.6.12 and 5.1.6
2. Japanese Pharmacopoeia (JP): edition 15, 9/2007, [English version (1/2009)], Chapter 4.05
3. United States Pharmacopeia (USP): edition USP32-NF27, 5/2009, Chapters <61> and <1223>
4. Parenteral Drug Association, May/June 2000, 54 (3), 1–39
5. FDA guidance documents located at www.fda.gov/RegulatoryInformation/Guidances/default.htm

Celsis
a charles river company

celsis.com

For Inquiries:
600 W Chicago Avenue, Suite 625, Chicago, IL 60654 USA **T** +1 312 476 1282 **F** +1 312 476 1201 **E** RDinfo@celsis.com
Boulevard A. Reyers, 70 B, 1030 Brussels, Belgium **T** +32 (0) 2 534 08 91 **F** +32 (0) 2 534 16 42 **E** RDinfo@celsis.com