Celsis
a charles river company

Qualifying and Validating the Celsis Rapid Detection System

A Celsis Rapid Detection Report

Many thousands of different materials and products are rapidly screened for microbial quality with Celsis systems every day – yours can be too. Celsis has experience that you can count on, with many hundreds of systems in use worldwide. Since 1992, we've been helping consumer product and pharmaceutical companies realize the tremendous operational and financial benefits of rapid methods. We're ready to help you every step of the way.

This report provides an overview of the common considerations and steps in qualifying and validating the Celsis rapid detection system.

Smart science for smart business™

Why Qualification and Validation are Important

Whether you are testing a product for the first time or replacing an existing microbial test method, the process of implementing your new Celsis rapid detection system will provide a high degree of assurance that the complete system will work reliably and consistently when in use. This is accomplished in two steps: qualification and validation.

Qualification is related to the instrument itself; it ensures that the Celsis equipment has been properly installed and is performing according to established specifications. Included as part of the instrument package, an installation qualification and operational qualification (IQ/OQ) is performed and documented by a Celsis technical support representative.

Validation is related to the intended application of the method; it establishes documented evidence that the Celsis assay will consistently perform according to intended operating conditions. Celsis provides a step-by-step validation guide to assist with the process.

In short, qualification and validation together prove that the Celsis system—including the equipment and the Celsis assay—does what it purports to do and, with proper maintenance, will continue to do so over time.

Qualification

The qualification process typically consists of three parts:

- **Installation Qualification (IQ)** – Establishes that the Celsis Advance is installed properly and will be used within the recommended physical and environmental conditions.
- **Operational Qualification (OQ)** – Establishes that the Celsis Advance operates under relevant operational conditions.
- **Performance Qualification (PQ)** – Performed on a periodic basis during normal usage, confirms that the Celsis Advance remains qualified.

An IQ/OQ is performed and documented by a Celsis technical support representative during the initial, on-site installation of Celsis equipment. PQ often includes the use of Celsis daily controls and periodic maintenance.

Validation

Validation provides a high degree of assurance that the method will consistently perform according to specification. A validation plan is often used to define the activities, procedures and responsibilities during the validation. This includes performing a risk assessment, defining what testing is required and determining the acceptance criteria. Upon completion of testing, a validation report is issued that summarizes the deliverables and activities and provides evidence that the method is validated.

You may also choose to supplement your validation with Celsis Technical Reports and/or reference to Celsis Drug Master Files (DMF).

To ensure that you are able to realize the value of the Celsis system as quickly as possible, Celsis offers optional lab services to assist in your validation efforts; from preliminary sample preparation and protocol development studies in our Rapid Detection Applications Lab to more formal method validation and documentation provided by the accredited, CGMP facilities of Celsis Analytical Services.

Guidelines for Validating Rapid Microbial Methods (RMM)

In addition to the **Celsis Validation Guide**, a number of validation guides for alternate microbiological test methods exist:

- **Parenteral Drug Association Technical Report 33**, "Evaluation, Validation and Implementation of New Microbiological Testing Methods"

- **United States Pharmacopeia (USP) Chapter <1223>**, "Validation of Alternative Microbiological Methods"
- **European Pharmacopeia (Ph EUR) Chapter 5.1.6**, "Alternative Methods for Control of Microbiological Quality"

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

A review of USP <1223> is provided by former USP member David Porter in his article, "Review of USP Chapter <1223> Validation of Alternative Microbiological Methods," American Pharmaceutical Review, March/April 2007, 10 (3), 76–81. Following is an excerpt from the article:

> *"(V)alidation of an alternative method to a compendia method is comparative in nature.... The requirement is that the alternative method results be equivalent or better than the compendia method results."*

Validating the Celsis Assay

The Celsis assay is a qualitative method where the result is one of two possible outcomes, positive or negative. This binary result simplifies the validation to a matter of demonstrating capability according to the following criteria:

- **Specificity:** The ability of the assay to detect a range of micro-organisms.
- **Limit of Detection:** The lowest number of micro-organisms in a sample that the test can detect (prior to any incubation).
- **Ruggedness:** The degree of agreement between test results obtained by the analysis of the same sample under a variety of normal test conditions (e.g. different analysts, different day of testing and different reagent lots).
- **Robustness:** The measure of the test's capacity to remain unaffected by variations in method parameters. This provides an indication of the test's reliability during normal usage.

Ph EUR 5.1.6 includes a fifth condition for qualitative assays:

- **Equivalence:** A measure of how similar the proposed test results are to results using the traditional method.

The guidelines also allow that the RMM vendor may provide vendor-generated validation data in lieu of or to supplement the user's validation data. Celsis provides this information in the form of Drug Master Files (DMFs) that are held by the FDA as well as through comprehensive Technical Reports that document validation of the method as outlined in the above-referenced guidance documents.

Finally, it should be noted that the testing parameters are typical of validation requirements of analytical test methods and are not unique to RMM validations.

Validating Your Products on the Celsis System

Product validation demonstrates the suitability of screening a product on the Celsis system and includes:

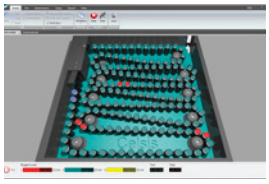
- **Sample Effects:** The sample effects protocol demonstrates whether the samples contain high levels of non-microbal ATP or whether the product formulation interferes with microbial detection by Celsis reagents.
- **Spiking Study:** The spiking study confirms the ability of the test to detect microbial contamination in product suspensions. The level of the microbial contamination is at the individual user's discretion.

- **Parallel Testing:** The purpose of parallel testing is to verify the Celsis method for routine use. The Celsis rapid screening method is carried out on a number of routine production batches alongside the traditional method. The number of samples to be assayed in parallel will depend on your user requirements and those of any regulatory body.

Product Groupings

It is an accepted practice to perform validations on similar products through a grouping technique. Rather than performing a validation on every product, one would evaluate the various products and select representative product types for validation. Groupings should be based on preservative content, product formulation and product matrix type. This approach can save considerable time and money while reducing testing redundancy. As new products are developed, a product grouping approach can replace the need to validate each new product separately.

Micro-organisms



Standard practice to confirm the ability of a method to detect contamination is by inoculating product suspensions with known organisms. During this part of the validation process, the conventional plate method is used as confirmation. The first step is to select the range of micro-organisms to be tested.

Indicator organisms and inoculum levels that are relevant to the product, product specification and manufacturing conditions should be selected. Micro-organisms frequently used for validation purposes include:

- Gram positives such as *Staphylococcus aureus* ATCC 6538
- Gram negatives such as *Escherichia coli* ATCC 8739 and *Pseudomonas aeruginosa* ATCC 9027
- Yeast such as *Candida albicans* ATCC 10231
- Mould such as *Aspergillus brasiliensis* ATCC 16404

Other organisms may be chosen based on environmental and facility isolates, micro-organisms common to previous contamination events, or micro-organisms common to product type or product usage.

Regulated Products

For regulated products, it is important to refer to current regulatory requirements and guidelines from the appropriate agency before embarking on a validation program. Depending on the product and how it is regulated, validation data may need to be submitted to a regulatory agency or be available for inspection. For example, the U.S. Food and Drug Administration (FDA) makes available a Comparability Protocol approach to streamline the submission and approval process.

Maintaining the Validated State

Once the Celsis system has been accepted, there are simple procedures for managing and maintaining the system in optimal condition. Your formal operation plan may include system training, service, system management, back-up and change control. Ongoing service and support is available globally from Celsis, including refresher training for new employees.

For additional information, contact Celsis Customer Support, +1 312 476 1282.

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