



Container Closure Integrity Testing Dye Ingress and Microbial Immersion

As the driving forces behind safety evaluation of materials and container closure systems in the U.S., the United States Pharmacopeia (USP) and Food and Drug Administration (FDA) enforce stringent testing requirements for container closure systems.

A critical step in understanding the biological safety and suitability of a container is the ability to characterize the materials and chemicals that have the potential to migrate through container closure system components and contaminate the drug product. Establishing a safe container closure system is as equally important as the contents of the container itself.

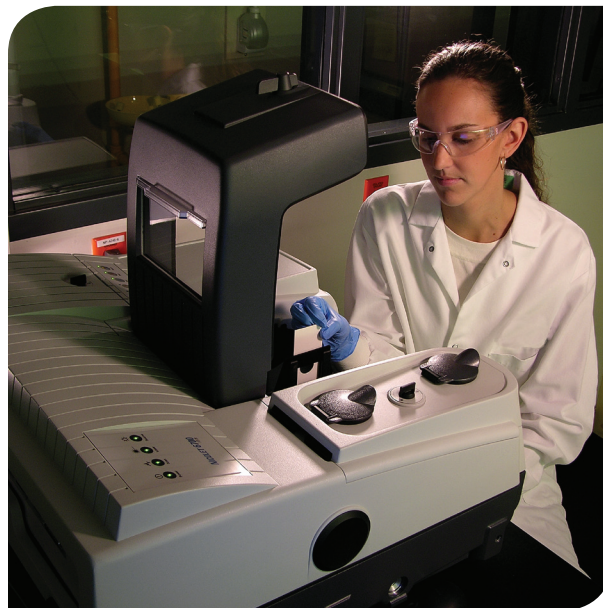
Why Choose Lancaster Laboratories?

- Lancaster Labs has more than 15 years of experience developing and executing methods for various container types.
- We have completed hundreds of container closure testing projects.
- We provide quick turnaround time on method development for dye ingress testing (in as little as two weeks).
- We offer generic in-house procedures, as well as customized approaches for microbial immersion testing.

Key Factors for Dye Ingress Testing

The method that is developed for dye ingress testing depends on several factors:

1. The type of product that is in the container will determine the dye that will be selected.
2. The fill volume of the container will determine the amount of dye added for controls.
3. If the product is lyophilized, the volume that it will need to be reconstituted to determine the dye amount added for controls.
4. The type of container closure being tested to determine vacuum pressure ranges and total volume required for submerging of the containers.

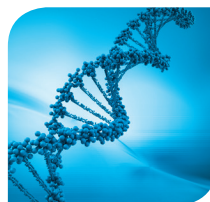


5. The type of dye selected for the tests must exhibit a strong absorbance over a region of wavelengths and must also be compatible with the sample matrix. Most dyes are prepared in water, although adjustments to the dye penetration can be made during the development process. Brilliant Green and Methylene Blue are two dyes that we consistently use.

Key Factors for Microbial Immersion Testing

The method that is developed for microbial immersion testing depends on several factors:

1. The type and size of the container will determine the immersion approach.
2. The media fill can determine if dye ingress is more appropriate than microbial immersion.
3. The challenge organism selection can be influenced by client preference or product formulation.
4. Immersion conditions under vacuum or static are determined by container type or delivery system.



Dye Ingress Methods

In order to develop the best method for your container closure project, we begin by determining whether the approach should be validated or non-validated (or qualified). Qualifications are not performed under protocol unless requested, but must prove the method to be scientifically sound. Typically, infor-

mation-gathering studies or bulk-product studies do not require validation of the method, and therefore, qualifications are used. This non-validated approach is also used for any drug product prior to Phase II. Once a product reaches Phase II, we recommend the validation approach, which can involve one of two techniques—visual or UV.

Visual vs. UV Dye Ingress Technique

	Visual	UV
Fill Volume	Used for containers with less than a 3 mL fill volume.	Requires a minimum fill volume of 3 mL.
Amount of Containers Needed	Requires approximately 75 containers for Method Development and Validation purposes.	Requires approximately 150 containers for Method Development and Validation Purposes* *Depending on what is determined during Method Development, more vials may be requested.
System Sensitivity and System Suitability Requirements	Requires a system sensitivity solution. This will use a vial spiked with a set concentration of dye.	Requires a system-suitability <u>and</u> system-sensitivity solution. Both of these solutions need to be prepared using the sample matrix. Bulk material or extra containers may be requested to fulfill this requirement.
Vacuum	After the positive controls and sample containers are placed into the dye bath, a vacuum is applied to obtain a manometer reading lower than 635 mmHg for 2 minutes, accurately timed.	After the positive controls and sample containers are placed into the dye bath, a vacuum is applied to obtain a manometer reading lower than 635 mmHg for 2 minutes, accurately timed.

Microbial Immersion Methods

Generic in-house methods are available and may be customized based on individual testing requirements.

Microbial Immersion Techniques

	Standard Approach	Customized Approach
Vacuum or Static	Vacuum approach is standard.	Container type may require static approach.
Challenge Organism	Standard method uses challenge organism recommended by Lancaster Labs.	Client requested/specified based on need.

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