Why Industry Cannot Just “Move Away" from the Dye Ingress Test

by Klaus Wuchner, Janssen, et al. May 5, 2021

A recent article in the *PDA Letter* ***(1)*** argued that the pharmaceutical industry should stop using the ubiquitous dye ingress test. The authors of this response would like to present an alternative view—that the industry should not limit its testing options if those extensively used and accepted methods are still useful and appropriate tools for ensuring patient safety.

The industry approach to CCIT has indeed changed over the last 50 years, driven by concern for patient safety. A significant change, beyond just the development of CCIT methods, has been a more holistic approach toward prevention of CCI issues. Instead of testing only the final product configuration, the focus has been an end-to-end approach to ensure a more robust and high-quality parenteral product through:

- Appropriate design of the container closure system (CCS)
- Development testing for robustness of the design
- Control of components
- Validation and control of the manufacturing process
- Assessment of CCI over product shelf life and throughout the product lifecycle

Along with this global improvement in CCI strategy, CCIT methods also have changed with the introduction of new testing technologies and equipment and the further development of existing methods, such as dye ingress.

For example, many pharmaceutical companies and contract testing laboratories have been able to successfully develop and qualify dye ingress methods for certain configurations with appropriate sensitivity. This, in part, explains why it remains the most commonly used CCIT method in the industry.

The frequent use of a single 2009 PDA JPST reference on dye ingress testing ***(2)***, based on a single case study that indicated certain limitations in the results, does not mean that all dye ingress methods for all product configurations will have those same limitations.

The most important factor of any test method is that it is well developed, qualified, validated and fit for its intended purpose ***(3)***.

With the wide range of primary container configurations and the various product types currently in the market, it is critical that all appropriately developed and qualified CCIT methods remain available as tools to be used to ensure a safe product for our patients.

All current CCIT methods, including deterministic methods, have their ideal applications and inherent limitations ***(4)***. For example, vacuum decay methods can fail to detect leaks in containers filled with high-protein concentration liquids due to clogging of the leak.

Similarly, a high voltage leak detection method might not be ideal for testing for a defect under the rigid needle shield of a prefilled syringe. Likewise, a laser headspace analysis method would be inappropriate for testing a product where a leak would not result in a change in headspace composition.

Although certain methods, like dye ingress, may be considered more traditional and do not require expensive new equipment, in some cases, they still may perform better than deterministic methods. In addition, liquid ingress methods present the advantage (if appropriately developed) to directly probe a common condition for microbial contamination, that is, the leak/defect needs to be filled with a liquid to allow microorganisms to penetrate through a defect into a CCS. There is no single CCIT gold standard but rather complementary technologies, including dye ingress, that allows the industry to appropriately test products during their lifecycle ***(4)***.

In conclusion, the pharmaceutical industry is definitively encouraged by the ongoing development of new CCIT method options, but it should not limit itself in the selection of method options.

Rationale for method selection should focus on consideration of whether newer methods offer superior performance in all conditions and configurations, and whether implementation of the newer method would result in measurably enhanced product quality and safety.

References

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