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Featured Application

Proactive Versus Reactive Testing For Glass Delamination in Pharmaceuticals

Introduction

Although guidance documents, such as USP <1660>, exist to provide recommendations to pharmaceutical companies related to glass delamination, the documents provide only recommendations rather than providing a specific protocol as it relates to exact drug products and potential containments. USP <1660> describes a methodology for evaluating various glass vials under simulated conditions. The results from these types of approaches can be difficult to translate to the issue of compatibility of a specific drug product with specific vial types in real-life scenarios. USP <1660> should be utilized as a guidance document, when a drug company has a known product and wants to evaluate compatibility with a specific vial type. This proactive approach attempts to understand the potential or likelihood of delamination when a specified drug product interacts with the interior surface of the selected glass vial. In other words, a proactive approach attempts to answer the question, ***"What is the compatibility of this drug with a known vial type?"*** One limitation of USP <1660>, having a bearing upon this proactive approach, relates to the setup and simulated accelerated stability testing of the product. This is an area that must be evaluated independently for each specific drug product. In addition to the actual testing methodology, the following questions often arise:

- **What FDA requirements, recommendations and guidelines exist?**
- **What are the size criteria for glass lamellae?**
- **Are there failure and/or acceptance criteria?**
- **How many samples should be analyzed per lot and per batch?**

Such questions are typically asked during the controlled test environment described in USP <1660> and in the characterization tests when testing is initiated on drug product. A reactive approach to glass delamination occurs when a product is evaluated for the presence or absence of glass lamellae in a released drug product. A reactive approach answers the question, ***"Is this drug product currently undergoing the process of delamination?"*** In these cases, some of the analytical techniques recommended in USP <1660> are utilized to determine the presence or absence of glass lamellae. Many of the recommendations, however, that are used solely as vial selection criteria are irrelevant when analyzing finished product for glass delamination.

Methods for Proactive Delamination Testing

"What is the compatibility of this drug with a known vial type?"

The proactive approach to delamination testing is intended for the durability testing of a given glass container that is filled with a specific final formulation of a drug product.

This allows an aggressive investigation to determine the suitability of a specific type of glass and glass container to house the drug product over the life of the drug. The most extreme circumstances that the container/drug product combination will be exposed to are tested to determine the propensity to cause glass lamellae in solution. This type of testing and the methods employed are what are addressed by USP <1660>, "The Evaluation of the Inner Surface Durability of Glass Containers."

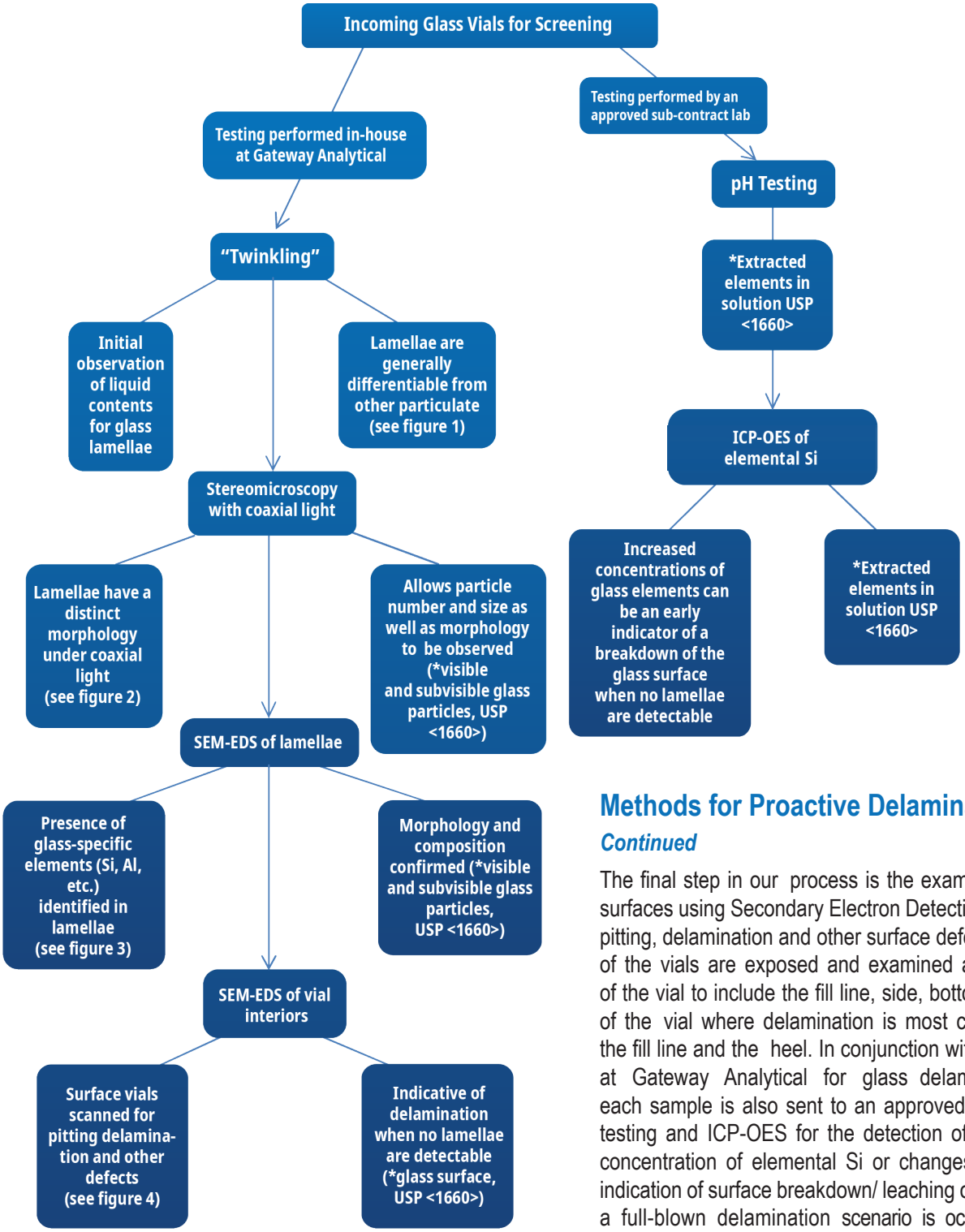
USP <1660> gives recommendations for predictive screening methods as described in the table below - *Table Courtesy of USP <1660>*

TABLE 1: Analytical Techniques for Screening Studies

PARAMETER	TEST PARAMETER	INSTRUMENTATION
Glass Inner Surface	• Degree of surface pitting • Chemical Composition as a function of depth	• DIC Mircroscopy or EM • SIMS
Extracted Elements in Solution	• Conductivity/pH • SiO_2 concentration	• Conductivity/pH meter • IC-MS or ICP-OES
Lamellae and Visible and Subvisible Glass Particles	• Presence of lamellae and visible particles • Lamellae or particle number and size • Lamellae or particle morphology and composition	• Visual inspection • Particle size analyzer • SEM-EDX

The typical approach to glass delamination examination is composed of four primary steps of analysis. The first step is a stereomicroscopic examination of the liquid vial contents using a bifurcated light source (figure 1). Glass lamellae tend to catch the light differently than other particulate and can be distinguished by this "twinkling" effect. The liquid vial contents are then filtered onto a polycarbonate filter, and the filter is examined using a stereomicroscope equipped with a coaxial light source. The very thin, and otherwise undetectable, lamellae are visible under the coaxial light source. If lamellae are observed, the filters are then placed in the SEM for elemental confirmation of the lamellae.

Gateway Analytical Approach to USP <1660>



Methods for Proactive Delamination Testing

Continued

The final step in our process is the examination of the inner vial surfaces using Secondary Electron Detection mode of the SEM for pitting, delamination and other surface defects. The inner surfaces of the vials are exposed and examined at representative areas of the vial to include the fill line, side, bottom and heel. The areas of the vial where delamination is most commonly observed are the fill line and the heel. In conjunction with the testing performed at Gateway Analytical for glass delamination, a portion of each sample is also sent to an approved subcontract lab for pH testing and ICP-OES for the detection of silicon. The increased concentration of elemental Si or changes in the pH can be an indication of surface breakdown/ leaching of the vial surface before a full-blown delamination scenario is occurring, and before any lamellae are able to be observed.

For a thorough USP <1660> approach, it is recommended to test a minimum of three lots of the drug product in at least two different vial types. Testing should also occur at several time points from the time of fill to the expected expiration date. Some companies even prefer to go one step further and select an additional time point that extends past the expiration date. Various changes in pH and temperature can also be employed as part of an accelerated test protocol for a more extensive determination of the propensity of the vial to delaminate while filled with the drug product of interest. When a thorough investigation is performed before the drug product is placed in circulation, assurance of a safe drug product being delivered to the customer can be achieved. While an extensive predictive screening test method for glass delamination can be time-intensive as well as expensive, the benefits of avoiding a total lot recall and post-delamination investigation far outweigh the costs.

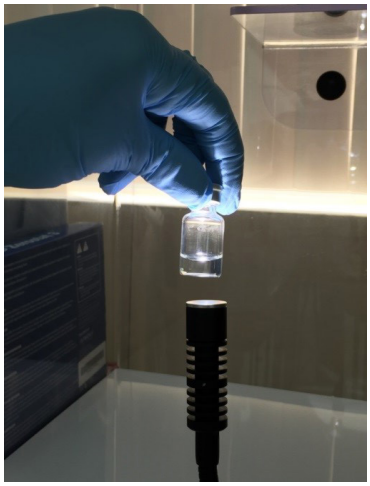


FIGURE 1: "Twinkling" - stereomicroscopic examination of vial contents using a bifurcated light source

Methods for Reactive Delamination Testing

"Is this drug product currently undergoing the process of delamination?"

In contrast to a predictive screening method, a reactive approach to glass delamination testing specifically tests for the presence of lamellae in solution and breakdown of the vial surface, when a drug product has already been manufactured and put into circulation. When glass delamination is indicated or suspected, a less-extensive and more cost-effective approach is recommended. For this type of sample, only certain tests are routinely performed. This includes the stereomicroscopic examination of the liquid vial contents for twinkling, stereomicroscopic examination of the filter using the coaxial light source (figure 2), SEM-EDS confirmation of lamellae (figure 3) and the SEM examination of the vial interiors for pitting, delamination and other surface defects (figure 4). These samples are sufficient to confirm or reject the presence of active glass delamination in the examined vials from a particular lot.

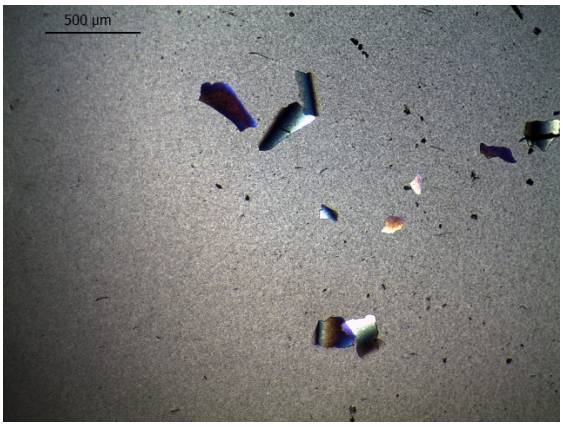


FIGURE 2: Stereomicroscopic examination of lamellae using a coaxial light source

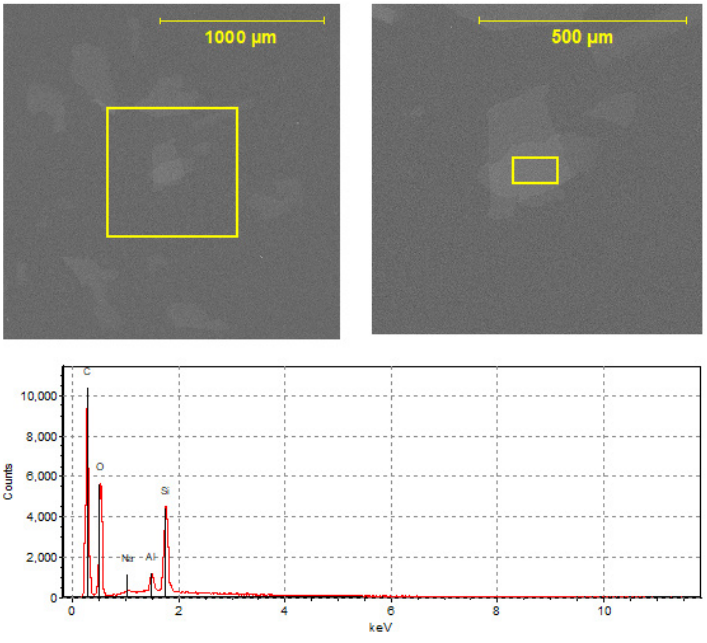


FIGURE 3: SEM-EDS examination of lamellae

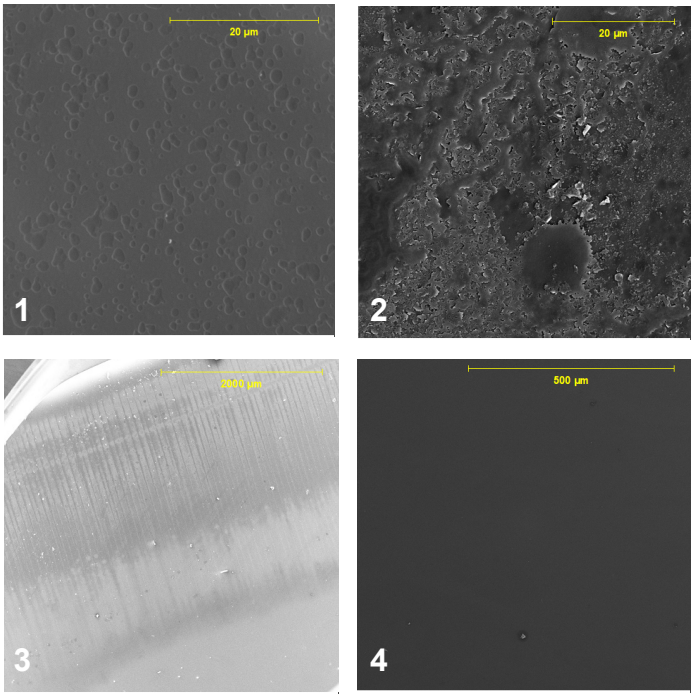


FIGURE 4: SED images of vial interiors (1: pitting, 2: delamination, 3: manufacturer defects, and 4: pristine surface

Discussion

We've seen the differences between methodologies for proactive glass testing utilizing the USP <1660> and characterization methods to determine potential identification of delamination in glass vials with finished product. We have also seen the variation of the USP <1660> method, when one needs to only understand if the presence of glass delamination exists. It is very important to understand which analytical techniques should be selected (and why) from the recommended analytical techniques proposed in the guidance document. One method that we do not typically utilize in routine glass delamination testing is the chemical composition as a function of depth, which can be addressed with Secondary Ion Mass Spectrometry (SIMS). Unfortunately, SIMS is a little-used method, and few laboratories with this capability operate under the FDA's Good Manufacturing Practices. Additional techniques that may provide similar types of information are Laser Induced Breakdown Spectroscopy (LIBS) or SEM-EDX mapping.

As mentioned earlier, a great number of factors can affect the durability of the surface of glass containers. These factors include glass composition, the conditions under which the containers were formed, subsequent handling and treatments, and the drug product in the containers. Due to the variety of causes of glass delamination and the causes that make glass susceptible to degradation and chemical changes, it is critical that all parenteral drug manufacturers consider a proactive approach to testing. In order to accomplish this, the process of the drug/vial interaction must be accelerated to simulate shelf life with the sample. Known accelerated product testing should be determined. For a typical drug stored at 25°C, every 30 days at 60°C is roughly equivalent to a full year of storage at 25°C (2). Our laboratory typically recommends at least 3–10 vials from each lot be evaluated.

The FDA does not currently have specified requirements or protocols for glass delamination testing beyond referencing the guidelines outlined in USP <1660>. The issue arises when a manufacturer has experienced a delamination issue and must evaluate the guidance of predictive study design to determine what methods are most acceptable to acquire a definitive conclusion of whether actual delamination has occurred in the product. This is the rationale for the modification of the USP <1660> method described above for final product testing.

Conclusion

Glass delamination is an ever-present issue within the parenteral drug industry. Many companies have taken a proactive approach to evaluate whether or not their drug product is compatible with specific vial containment for their specific product. This proactive approach focuses on the utilization of the USP <1660> guidance documents that provides a general study outline to complete this evaluation. However, when an issue of potential glass delamination arises in a final drug product, companies have to be reactive in their approach when determining the methodology for identifying glass delamination. The methodologies spelled out in USP <1660> do not focus on this latter scenario. Lastly, many significant questions still remain as to the required number of samples, number of lots, time points tested and specific analytical protocols that are actually required by the FDA.

References

1. USP <1660>
2. http://www.schott.com/pharma_services/english/download/delamination_pre-testing_contract_pharma_2013.pdf