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## BRIEFING

《 1660 》 **Evaluation of the Inner Surface Durability of Glass Containers.** In response to the recent product recalls that have further increased the pharmaceutical industry's heightened awareness of glass quality and glass delamination (i.e., the formation of glass flakes in a vial), USP proposes a new general information chapter to recommend approaches to predict potential formation of glass particles and delamination.

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*Add the following:*

# ▪ 《 1660 》 EVALUATION OF THE INNER SURFACE DURABILITY OF GLASS CONTAINERS

## PURPOSE

This general information chapter provides information about factors that affect the durability of the inner surface of glass containers and recommends approaches to predict the potential of a drug product to cause formation of glass particles and delamination and to detect their occurrence. Useful procedures are listed and can be applied for both characterization and control tests.

## SCOPE

This chapter addresses molded bottles and vials manufactured by molding; or ampules, cartridges, vials, and prefilled syringes manufactured from tubing glass. Glass for pharmaceutical packaging is classified as Type I borosilicate glass, Type II treated soda-lime-silica glass, or Type III soda-lime-silica glass on the basis of the hydrolytic resistance of the glass, as defined in [Containers—Glass](#) 《 660 》. Type I glass containers are suitable for most products for parenteral and nonparenteral use. Type II glass containers are suitable for most acidic and neutral aqueous products for parenteral and nonparenteral uses, and can be used for alkaline parenteral products when stability data demonstrate their suitability. Type III glass containers usually are not used for parenteral products or for powders for parenteral use, except when suitable stability test data indicate that Type III glass is satisfactory. This chapter focuses primarily on Type I glass, because it is the most widely used in the biopharmaceutical industry.

The chapter should be useful for the following:

- Contract manufacturing and filling organizations
- Molded and tubing glass container manufacturers and converters
- Pharmaceutical and biopharmaceutical companies

Glass, in the form of ampules, bottles, cartridges, vials, and prefilled syringes, is the

container material of choice for parenteral products. This is especially true for the biopharmaceuticals that have increased the demand for small-volume glass cartridges, vials, and prefillable syringes. Glass delamination, which ultimately results in the appearance of lamellae, is a serious quality issue and can result in a product recall. Delamination with the appearance of glass lamellae is a lagging indicator of structural instability. Although delamination is the most obvious visual indicator, it represents the final stage of a seriously weakened glass surface structure, and can be observed only at a point where prevention is no longer an option. In addition, mechanical energy from shaking or vial-to-vial contact may dislodge the lamellae from the weakened internal surface.

Tests for delamination combine an examination of the vial surface and analysis of an aggressive test solution to predict the propensity of the internal glass surface of vials to delaminate. Indicators include the appearance of a pitted, fractured surface instead of a smooth surface, as well as a number of changes in the test solution, including increases in  $\text{SiO}_2$  concentration, the ratio of  $\text{SiO}_2/\text{B}_2\text{O}_3$  or  $\text{Si}/\text{Al}$ , the number of subvisible particulates in the solution, and a fall in pH.

### GLASS TYPES

Glass in its pure form consists of silicon dioxide with a melting point of approximately  $1700^\circ$ . Added network modifiers, such as sodium and potassium oxides or boric oxide, lower the melting point, while other network stabilizers, such as calcium and aluminum oxides, improve the durability of the glass. Colored glass (e.g., amber glass) is produced by transition metal oxides such as iron oxides. All additives to pure silicon dioxide can be viewed as potential extractables in glass.

Glass compositions do not exist at a stoichiometric chemical composition but rather are expressed over a range of compositions. Thus, there is allowable variation within a glass type, and glass types may vary slightly among glass producers. Soda-lime-silica glass consists of silica (60%–75%), sodium and potassium oxides (12%–18%), and smaller amounts of calcium, magnesium, and aluminum oxides (5%–12%). This glass has a relatively high coefficient of expansion (COE) of  $8.4 \times 10^{-5}$  per degree and is susceptible to damage by thermic shock. Borosilicate glass consists of silica (70%–80%), boric oxide (7%–13%), and smaller amounts of sodium, potassium, and aluminum oxides. The presence of boron provides greater resistance to thermal shock and to hydrolytic attack. Type I glass is available in two formulations: 33 glass and 51 glass, in reference to their individual COEs of  $32.5 \times 10^{-7}$  per degree and  $51.0 \times 10^{-7}$  per degree, respectively.

### FORMATION OF MOLDED AND TUBING GLASS CONTAINERS

Formation of molded and tubing glass containers requires a number of steps. The quality of the container used in packaging depends on the conditions and the quality control of each step. Both molded and tubing glasses originate from a glass furnace, and different furnaces are dedicated to borosilicate or soda-lime-silica glass. The refractory bricks lining the furnace deteriorate with time and must be replaced. Worn bricks can contribute to cosmetic defects such as stones (inclusions in the glass) that become incorporated into the molded glass containers or glass tubing.

Molded glass vials and bottles are manufactured using a stream of molten glass cut to form a piece of glass that then enters a mold that shapes the container. Formation of containers from tubing glass is a two-step process. Glass tubes of a specific diameter are formed from a stream of molten glass that exits the furnace, is cooled, and is sectioned into standard lengths.

These tubes are subsequently converted into glass containers (ampules, cartridges, syringes, or vials) by either the glass manufacturer or by independent converters. It is technically difficult to form glass tubing with a diameter sufficient to make bottles containing 100 mL or more, so these containers are produced by molding.

Gas flames are used to soften tubing glass to form the neck, to melt the glass to form the ampuls or vial base, and to separate the container from the glass tube. In the case of cartridges and prefillable syringes, the glass tube is cut to length, and the ends are softened to form the nozzle and flange of the syringe and the neck and rear of the cartridge. Heating rate, maximum glass temperature, and production speed are critical parameters that can be adjusted for individual forming machines. After formation, both tubing and molded containers pass through an annealing oven (lehr) that heats the containers to approximately 570° and then gradually cools them in order to remove stresses in the container due to the manufacturing process. This too is a critical process because poorly annealed containers show reduced durability.

The process of forming tubing vials and ampules has an effect on the local surface composition of the glass. During formation of the neck and particularly the base, the temperature of the inner surface of the containers can exceed the evaporation point of some of the glass components such as alkali borates. Under certain time–temperature conditions, the glass can phase separate during forming, creating nonhomogenous surface chemistry on the interior of the container. Both scenarios are undesirable for the storage of aggressive liquids from a surface durability perspective. Evidence of this can be obtained by appropriately etching the glass with acid, after which an opaque ring will appear above the heel of the container, indicating a negative change in the inner surface chemistry. The same phenomenon can be observed at the shoulder of the container as well, but in many instances this area does not experience prolonged contact with a liquid.

Glass also is reheated during depyrogenation and sterilization, both before and after filling during terminal sterilization. The temperatures used for these steps are below those used for forming and annealing (see [Table 1](#)), and do not pose an additional risk to the durability of the glass from phase separation volatilization. The chemical durability of the glass can also be compromised by the presence of water during these unit operations, because water can diffuse into the glass and disrupt the silicate structure.

**Table 1. Temperatures Encountered During Formation and Processing of Type I Tubing Glass Containers**

<b>Key Operations</b>	<b>Typical Temperatures (°)</b>
Furnace	1650
Sectioning of tube and base formation	1370
Working range	1000–1200
Softening	827
Annealing	570
Depyrogenation range	250–350
Terminal sterilization	121

At times, the inner surfaces of glass ampules, vials, and bottles undergo additional treatments. As an example, heating glass propagates sodium oxide toward the inner surface of the container, but washing with water does not remove sodium oxide because of the latter's

limited solubility. Over time, sodium ions migrate into the solution in the container and produce hydroxide ions, resulting in an elevated pH in unbuffered solutions. Treatment with ammonium sulfate converts the sodium oxide on the inner surface and to a depth of a few angstroms into highly soluble sodium sulfate that then can be removed by washing. Although removal of sodium ions from the surface does reduce the propensity for pH shift, published work also has shown that the treatment weakens the inner surface by removing structural elements, leaving a silica-rich layer. The process originally was designed to raise the surface hydrolytic resistance of Type III soda-lime-silica glass to that of Type II glass in order to mimic the hydrolytic resistance of Type I glass. This process also can be applied to Type I glass. In a further example, treatment of the internal container surface of Type I glass with pure silica improves the container's durability.

In summary, the key factors that influence the glass surface durability of containers manufactured from Type I glass (the type most often used for parenteral drugs) are manufacturing conditions such as the forming temperature, the time of exposure to heat, and the annealing conditions, plus any additional treatments after formation, such as the use of ammonium sulfate. Storage in humid conditions and processing operations at the pharmaceutical manufacturer, especially depyrogenation in the presence of water vapor and terminal sterilization via autoclaving, also have been shown to reduce the chemical resistance of glass.

### GOOD GLASS SUPPLY-CHAIN PRACTICES

Before considering treatment of glass containers, manufacturers should consider the upstream provenance of the containers they purchase. Thus, to maintain and improve container quality over time, manufacturers should take a number of steps when they select a glass container vendor.

- Audit supplier (glass manufacturer or converter)
- Obtain glass formulation from the supplier
- Designate 33 or 51 COE for Type I glass
- Determine tubing glass source(s) for converters
- Determine production site(s)
- Determine if the tubing converting equipment varies in age, design, and manufacturer from site to site
- Evaluate in-line electronic inspection systems for quality control of glass tubing and for glass containers
- Determine whether the containers have been treated with ammonium sulfate
- Establish acceptable quality levels for incoming lots with the vendor
- Monitor and trend the quality of incoming batches by monitoring the values obtained by the *Surface Glass Test* in [660](#)

### GLASS SURFACE CHEMISTRY

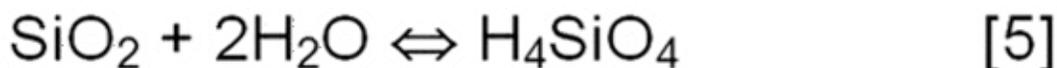
After manufacturers are assured of the quality and consistency of the glass containers they purchase, they can use the complex aqueous chemistry of surface glass to decide on potential drug product formulation and treatment steps that could increase glass stability. The reaction between the glass surface and an aqueous phase (water or water vapor) involves ion exchange between hydrogen ions and alkaline ions in the glass (*Equation 1*) and diffusion of water into the glass (*Equation 2*). This results in hydration of the glass surface and an alkali-depleted, silica-rich layer.



The presence of water in the leachate promotes hydrolysis of the Si–O bond (*Equation 3*) and condensation (*Equation 4*), forming a silica-gel layer.



The mechanical properties of the surface gel that forms are different from those of bulk glass. Repeated hydration and dehydration of the layer leads to the cracking of the gel layer and eventual generation of particles. This process is worsened as the gel layer increases in thickness. This phenomenon is well known in glass exposed to ambient moisture (known as weathering). At higher pH values, the mechanism of glass degradation changes from the leaching of alkali elements to the dissolution of the silicate network as shown in *Equation 5* and *Equation 6*.



Reaction (*Equation 6*) increases the solubility of the silicic acid in solution, driving the reaction forward. At some point the limit of solubility is exceeded, and subvisible particles are formed. If the solution is not buffered, a decrease in the solution pH will take place. These reactions and scenarios apply only to the reactions of glass with water; the presence of drug product formulations can complicate the situation considerably.

### FACTORS THAT INFLUENCE INNER SURFACE DURABILITY

A number of factors have the potential to influence the durability of the inner 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 container ([Table 2](#)). Not all listed factors influence surface durability to the same degree, and their effects can be additive. Because of the range of variables, end users should examine all relevant variables for an individual drug product and assess the degree of risk for delamination and formation of subvisible and visible glass particles. Delamination is the process whereby thin layers of glass—described as either flakes or lamellae—are detached from the inner surface of a container. In some situations, the accumulation of risk factors indicates that a glass container should not be used for a particular formulation.

**Table 2. Factors That Influence the Inner Surface Durability of Glass**

Container	Container Storage, Handling, and Processing	Drug Product
<ul style="list-style-type: none"> <li>• Glass composition</li> <li>• Molded or tubing</li> </ul>	<ul style="list-style-type: none"> <li>• Post-formation treatments:</li> </ul>	<ul style="list-style-type: none"> <li>• Drug substance</li> <li>• Formulation:</li> </ul>

container <ul style="list-style-type: none"> <li>• Manufacturing process:             <ul style="list-style-type: none"> <li>- Converting speed</li> <li>- Converting temperature</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>- Ammonium sulfate</li> <li>• Storage conditions:             <ul style="list-style-type: none"> <li>- High humidity</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>- Acetate, citrate, phosphate buffers</li> <li>- Sodium salts of organic acids, e.g., gluconate, malate, succinate, tartrate</li> <li>- High ionic strength, e.g., &gt;0.1 M of alkaline salts</li> <li>- Complexing agents, e.g., EDTA</li> <li>- High pH, e.g., &gt;8.0</li> <li>• Terminal sterilization</li> <li>• Labeled storage conditions (refrigerated or controlled room temperature)</li> <li>• Shelf life</li> </ul>
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### SCREENING METHODS TO EVALUATE INNER SURFACE DURABILITY

Each lot of Type I glass containers received by a pharmaceutical manufacturer must comply with the *Surface Glass Test* in chapter [\(660\)](#). This test provides an indication of surface durability but does not appear to provide a clear direct correlation with the propensity to form glass particles or to delaminate. A low surface alkalinity value can be obtained from containers treated with ammonium sulfate; but the treatment itself may reduce the inner surface durability, and the amount of alkalinity comes from the sum of all the internal surfaces. Although this is representative for all internal surfaces of molded glass containers, tubing glass containers can have different degrees of surface durability, depending on the location (e.g., just above the heel vs. the side wall). The most important variable that affects the surface durability is the drug product itself, and because it uses water as the extracting medium, the *Surface Glass Test* does not take this into consideration. Therefore, the *Surface Glass Test* represents only a first step in quality control of surface durability, and additional screening methods should be used to demonstrate the suitability of vials for a formulation from a particular source before formal stability studies begin.

#### Predictive Screening Methods

Screening methods help evaluate glass containers from different vendors (molded or tubular), glass formulations (COE 33 or 51), and post-formation treatments. Screening also establishes lot-to-lot variation from individual vendors during the drug development process, as well as lot-to-lot variations for products that have been shown to have a particular propensity to form glass particles or to delaminate. Screening methods can use a number of different technologies to examine three key parameters: visual examination and chemical profile of the inner surface layer, the amount and identity of extracted elements in solution, and the number of subvisible and visible particles in solution. Taken together, these elements are assessed by predictive tests for formation of glass particles and delamination, processes that reflect reduced durability. Predictive tests should look for precursors that lead to delamination rather than flakes themselves, and should be able to quickly provide predictive indication of surface durability. This makes the tests useful not just for vendor selection but also for evaluation of individual lots if necessary. Some of the more commonly used analytical methods for evaluating the three key parameters are shown in [Table 3](#).

**Table 3. Analytical Methods for Screening Studies**

Parameter	Test Parameter	Analytical Methods
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Glass surface	<ul style="list-style-type: none"> <li>• Degree of surface pitting</li> <li>• Chemical composition as a function of depth</li> </ul>	<ul style="list-style-type: none"> <li>• DIC Microscopy<sup>a</sup> or EM<sup>b</sup></li> <li>• SIMS<sup>c</sup></li> </ul>
Extracted elements in solution	<ul style="list-style-type: none"> <li>• Conductivity/pH</li> <li>• Individual and total extractables <ul style="list-style-type: none"> <li>- SiO<sub>2</sub> concentration</li> <li>- SiO<sub>2</sub>/B<sub>2</sub>O<sub>3</sub> or Si/Al ratio</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>• Conductivity/pH meter</li> <li>• IC-MS<sup>d</sup> or ICP-OES<sup>e</sup></li> </ul>
Visible and subvisible glass particles	<ul style="list-style-type: none"> <li>• Particle number and size</li> <li>• Particle morphology and composition</li> </ul>	<ul style="list-style-type: none"> <li>• Particle size analyzer</li> <li>• SEM-EDX<sup>f</sup></li> </ul>
<p><sup>a</sup> Differential interference contrast microscopy.</p> <p><sup>b</sup> Electron microscopy.</p> <p><sup>c</sup> Secondary ion mass spectrometry.</p> <p><sup>d</sup> Inductively coupled plasma-mass spectrometry.</p> <p><sup>e</sup> Inductively coupled plasma-optical emission spectrometry.</p> <p><sup>f</sup> Scanning electron microscopy-energy-dispersive X-ray spectroscopy.</p>		

### Aggressive Screening Conditions

In selecting an appropriate primary glass container for pharmaceutical liquids, analysts should consider two approaches. The first is a series of accelerated temperature exposures using aggressive conditions that establish, in rank order, the chemical durability of the container without any specific reference to a given compound. Such testing can be helpful when selecting a packaging kit for which the most chemically durable glass is desired. This testing also can be helpful in determining if changes in glass quality have occurred or in assessing processing changes that have been made by the primary container manufacturer. [Table 4](#) provides some model systems that could be used for this assessment.

**Table 4. Formulations and Conditions Used to Accelerate Delamination**

Formulation	0.9% KCl pH 8.0	3% Citric Acid pH 8.0	20 mM Glycine pH 10.0
Conditions	2 h at 121°	24 h at 80°	24 h at 50°

### Screening Strategy for Drug Products

If the purpose of the glass screening is to determine the suitability of a given glass container for a specific product, the testing proposed in [Table 4](#) is insufficient. The exposure conditions are too harsh and do not provide a direct link to the product itself. In these instances, accelerated conditions are still relevant, but they must link to the relevant conditions for the given product. For example, if a product will be stored at 5° and accelerated conditions are 30°, then testing should occur at 30°. Many products or formulations cannot withstand the elevated temperatures shown in [Table 4](#). In addition, false positive testing results could be obtained because the unusually high temperatures shown in [Table 4](#) could cause signs of delamination, but moderate exposure at 30° would produce no evidence of glass incompatibility.

Because lower temperatures are required for actual product testing, the duration of testing must be longer, ranging from weeks to months. A larger number of vials also is appropriate for this scenario because the goal of the testing is to ensure the results are representative of the

quality of the glass that will be used for the drug product. [Table 5](#) shows some of the conditions that could be used for testing with a specific product.

**Table 5. Screening Strategy for Glass Vials**

Water Control	Stress Test	Drug Product Control
<ul style="list-style-type: none"> <li>• Washed, depyrogenated container</li> <li>• Filled with Water for Injection</li> <li>• Autoclaved</li> <li>• Accelerated drug product stability storage conditions</li> </ul>	<ul style="list-style-type: none"> <li>• Washed, depyrogenated container</li> <li>• Filled with stress test solution</li> <li>• Accelerated treatment</li> </ul>	<ul style="list-style-type: none"> <li>• Washed, depyrogenated container</li> <li>• Filled with drug product</li> <li>• Autoclave if applicable</li> <li>• Accelerated drug product stability storage conditions</li> </ul>

## CONCLUSIONS

Evaluation of the internal surface of glass containers begins with the *Surface Glass Test*, which uses water as the extracting medium. A low value is not always an indicator of a durable inner surface because the results are obtained using surface treatments (e.g., ammonium sulfate). Such treatments can lead to a silica-rich surface layer that represents a weakened glass structure, and risk of delamination increases when the vial is filled with formulations that contain aggressive agents such as organic acids, EDTA, or solutions that have high ionic strength or pH. The screening methods and strategies described in this chapter can assist in the evaluation of glass containers from different suppliers and can provide an indication of the propensity of the selected formulation to cause delamination over time. Selection of glass vials intended to contain a drug product with one or more of the formulation risk factors identified in [Table 2](#) should undergo particular scrutiny.

## ADDITIONAL SOURCES OF INFORMATION

The references provide additional resources regarding the reaction of glass with solutions. They are not exhaustive but are intended to provide greater depth of information should the need arise.

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