BRIEFING

⟨1660⟩ Evaluation of the Inner Surface Durability of Glass Containers, *USP 40* page 2007. The Packaging and Distribution Expert Committee is proposing the following revision to clarify the intent of the chapter and provide additional information to aid in the understanding of the factors that affect the inner surface durability of a glass container. Listed below are the key changes being proposed:

1. The chapter title is changed to "Glass Containers Used in Pharmaceutical Packaging/Delivery Systems: Manufacture and Evaluation of the Inner Surface Durability".
2. The *Purpose* section is changed to an *Introduction*.
3. *Table 1* is added to include aluminosilicate glass.
4. The *Glass Surface Chemistry* section is revised and new equations added.
5. A new section is added on *Glass Particles and Flakes*.
6. New sections are added on *Critical Parameters in the Autoclave Loading Procedure*, *Trays*, *Autoclave Loads*, *Sample Types and Sizes*, and *Autoclave Calibration and Load Mapping*.

Additionally, minor editorial changes have been made to update the chapter to current *USP* style.

A workshop, *Modernization of USP Packaging Standards for Glass and Elastomeric Components*, will be held June 19–20, 2017 at USP in Rockville, Maryland, to discuss the revision proposals for this chapter and for *Containers—Glass* ⟨660⟩, also appearing in this issue of *PF* (for details of the workshop, go to the USP website www.usp.org/meetings-courses/workshops/modernization-usp-packaging-standards-glass-and-elastomeric-components).

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Correspondence Number—C185927

Change to read:

⟨1660⟩~~EVALUATION OF THE INNER SURFACE DURABILITY OF GLASS~~

~~CONTAINERS~~ GLASS CONTAINERS USED IN PHARMACEUTICAL PACKAGING/DELIVERY SYSTEMS: MANUFACTURE AND EVALUATION OF THE INNER SURFACE DURABILITY ▪1S (*USP41*)

Add the following:

▪1S (*USP41*)

Change to read:

~~PURPOSE~~ ▪INTRODUCTION. ▪1S (*USP41*)

This general information chapter ~~provides information about factors that affect the durability of the inner surface of glass containers. Recommended approaches are provided to evaluate the potential of a drug product to cause formation of glass particles and delamination of the inner surface. Screening methods are provided to detect glass particles and delamination, allowing a comparison to be made of glass durability on a lot-to-lot basis or between different glass manufacturers.~~ addresses bottles and vials manufactured by molding as well as ampules, cartridges, vials, and syringes manufactured from tubing glass. Glass containers used in pharmaceutical packaging are classified as being 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⟩.. 1S (*USP41*)

Change to read:

SCOPE

~~This chapter addresses bottles and vials manufactured by molding and ampuls, cartridges, vials, and prefillable 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 pharmaceutical and biopharmaceutical industry for parenteral products although the guidance can be equally applied to Type II and Type III glass used for parenteral products.~~

~~The chapter should be useful for the following:~~

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

~~Glass delamination may be described as the appearance of thin flexible flakes of glass (or lamellae) that can range in size from <50 µm to 200 µm in a drug product solution. This is a serious quality issue and can result in a product recall. The appearance of glass lamellae is a lagging indicator of a strong interaction between the drug product and the inner surface of the~~

~~glass. Although delamination is the most obvious visual indicator, it represents the final stage of a complex glass corrosion reaction, and can be observed only at a point where prevention is no longer an option. Adding further complexity to detection, mechanical energy from shaking or vial-to-vial contact during transportation may be required to dislodge the lamellae from the internal surface of a filled vial and facilitate observation.~~

~~Tests for delamination combine the visual examination of the solution, an examination of the vial's internal surface and analysis of an aggressive test solution to assess the propensity of the internal glass surface of vials to delaminate. These examinations and the use of an aggressive test solution are intended to be conducted by the pharmaceutical manufacturer, not the glass manufacturer or converter.~~

This chapter provides information on the formation, processing, and testing of glass containers used in pharmaceutical packaging/delivery systems and the factors that affect the inner surface durability. Screening methods are provided to detect glass particles and flakes, allowing a comparison to be made of glass durability on a lot-to-lot basis or between different glass manufacturers.. 1S (*USP41*)

Change to read:

GLASS TYPES

Glass in its pure form consists of silicon dioxide with a melting point in excess of ~~1700°~~ 2000°.. 1S (*USP41*) However, this is rarely used commercially because of the cost of working at these elevated temperatures. Added network modifiers, such as sodium, potassium, ~~or boron oxide~~ calcium, barium, and magnesium,. 1S (*USP41*) lower the melting point and lower the chemical durability, whereas added network stabilizers, such as ~~calcium~~ boron. 1S (*USP41*) 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, titanium dioxide and/or manganese oxide.. 1S (*USP41*) ~~All additives to pure silicon dioxide, as well as silicon itself, can be viewed as potential extractables from glass containers~~ Each component of glass containers is potentially the source for an extractable and/or leachable.. 1S (*USP41*)

Glass compositions do not exist as stoichiometric chemical compounds but rather are expressed by a range of compositions. ~~Thus, there~~ There. 1S (*USP41*) is allowable variation within a glass type, and glass ~~types may vary slightly~~ composition varies. 1S (*USP41*) among glass producers (see *Table 1*).

Table 1

Chemical Composition	Borosilicate Glass (wt%)	Aluminosilicate Glass (wt%)	Soda-lime-silica Glass (wt%)
Silicon dioxide	65–82	68–80	69–75
Boric oxide	5–13	—	0–1
Aluminum oxide	2–9	2–12	0.5–4
Sodium and potassium oxides	3–12	8–15	12–16
Calcium, magnesium, and barium oxides	0–6	3–10	10–15

.1S (*USP41*) Soda-lime-silica glass ~~consists of silicon dioxide (60–75 wt%), sodium and potassium oxides (12–18 wt%), and smaller amounts of calcium, magnesium, and aluminum oxides (5–12 wt%). This glass~~ . 1S (*USP41*) has a relative high coefficient . of thermal . 1S (*USP41*) expansion . (CTE; also abbreviated as . 1S (*USP41*) COE) of 80–90 × 10^{-7} per degree and is susceptible to breakage by ~~thermic~~ thermal . 1S (*USP41*) shock. ~~Borosilicate glass consists of silica (65–80 wt%), boric oxide (7–13 wt%), and smaller amounts of sodium, potassium, and aluminum oxides.~~ . 1S (*USP41*) The presence of boron . in borosilicate glass . 1S (*USP41*) provides greater resistance to thermal shock through a ~~reduction in COE~~ . lower CTE . 1S (*USP41*) and to hydrolytic attack by increasing the connectivity of the glass network. ~~Type I~~ . Borosilicate . 1S (*USP41*) glass is available in multiple formulations: tubular glass is available with a low ~~COE~~ . CTE, . 1S (*USP41*) described as 32–33 expansion glass and with a relatively low ~~COE~~ . CTE . 1S (*USP41*) (range, ~~48–56~~ . 49–55 . 1S (*USP41*) expansion), for example 51 expansion glass, in reference to their individual ~~COEs~~ . CTEs . 1S (*USP41*) of 32.5 × 10^{-7} per degree and 51.0 × 10^{-7} per degree, respectively. Molded glass has a higher ~~COE~~ . CTE . 1S (*USP41*) in the region of ~~60–63~~ . 55–64 . 1S (*USP41*) expansion.

Change to read:

FORMATION . AND PROCESSING . 1S (*USP41*) OF MOLDED AND TUBULAR GLASS CONTAINERS

Formation of molded and tubular 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 tubular containers originate from a glass furnace, and different furnaces are

dedicated to borosilicate, aluminosilicate, (1S (USP41)) 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 in a one-step process whereby a stream of molten glass is cut into a gob, which then enters a mold where air or tooling is used to shape the container to the mold. 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 tubing glass manufacturer or by independent~~ (1S (USP41)) 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 base of ampules or vials, and to separate the container from the glass tube. In the case of cartridges and syringes, the glass tube is cut to length, and the ends are softened to form the ~~nozzle~~ cone, (1S (USP41)) and flange of the syringe and the neck and ~~rear~~ bottom, (1S (USP41)) of the cartridge. Heating rate, maximum glass temperature, and production speed are critical parameters that ~~can~~ should, (1S (USP41)) be adjusted for individual forming machines. After formation, both tubular and molded containers are passed through an annealing oven (lehr) ~~that heats the containers to 20° to 30° above the transformation temperature (T_g) of the individual glass formulation (T_g for borosilicate glass is approximately 570°)~~, (1S (USP41)) and then gradually cooled. This process removes stress marks from the container surface produced during the manufacturing process. This too is a critical process because poorly annealed containers show reduced ~~chemical and~~ (1S (USP41)) mechanical durability.

The process of forming tubular vials and ampules has an effect on the local surface composition of the glass. During formation of the neck and particularly the ~~base~~ bottom, (1S (USP41)) the temperature of the inner surface of the containers ~~can~~ mostly, (1S (USP41)) exceeds 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 nonhomogeneous surface chemistry on the interior of the bottom of the, (1S (USP41)) container. Both scenarios are undesirable for the storage of aggressive liquids from a surface chemical 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.~~

~~PROCESSING OF MOLDED AND TUBULAR GLASS CONTAINERS~~

Surface Treatments

INNER SURFACE TREATMENTS. 1S (*USP41*)

~~At times, the inner surfaces of glass ampuls~~ A preliminary water washing of the inner surface can be applied to remove particles to improve optical inspection and to prepare the surface for further treatments. In certain cases it might be necessary to alter the properties of the inner surface of glass ampules, 1S (*USP41*) vials, and bottles that 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.~~ 1S (*USP41*) When glass is exposed to an aqueous solution, sodium ions diffuse into the solution from the glass surface to produce hydroxide ions, resulting in an elevated pH in unbuffered solutions. One common treatment is the use of ammonium sulfate which converts the sodium ~~oxide~~ 1S (*USP41*) on the inner surface to a depth of approximately ~~10–100 nm~~ 0.1–0.5 µm 1S (*USP41*) 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, the treatment does remove structural elements, leaving a thin silica-rich inner surface 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.

There are two additional treatments that are occasionally used together with ammonium sulfate for molded glass containers. These are the use of gaseous sulfuric acid at temperatures of about 500°. Another treatment applied in similar conditions as above, but less effective is the use of 1,2 difluoroethane which converts the sodium in sodium fluoride that sublimates during the glass annealing.

The inner surface of a glass container is rather hydrophilic and this can have a major influence on the adsorption of certain drugs, proteins and radiopharmaceutical products to the glass surface. The leaching of either an element or a compound from the glass container may affect the drug quality. Coating of the inner surface may prevent surface adsorption or elemental release. For example, a silicon dioxide (SiO_2) layer may be applied by techniques such as plasma impulse chemical vapor deposition (PICVD) or

plasma-enhanced chemical vapor deposition (PECVD) that fixes the coating permanently on the surface. The glass container along with the permanent coating must be evaluated by applicable quality tests.

Silicon is used as a lubricant in vials, syringes, and cartridges. In all cases the impact of silicon on the drug quality must be assessed.

OUTER SURFACE TREATMENTS

Glass containers may be subject to abrasion during conveyance on production lines and transportation resulting in scratching and bump checks that may adversely affect their mechanical resistance. Two processes are available to mitigate against these possibilities by strengthening the outer surface (hot treatment) and then by applying a lubricating layer (cold treatment).

Hot treatment: Mechanical strengthening of the outer surface of glass vials and bottles can be produced by adding a coating of tin oxide to this surface. This is produced by the chemical vapor deposition of monobutylin trichloride (MBTC) just after the container forming process. The temperature of glass at the time of the treatment is 400°–700°, transforming MBTC to tin oxide by oxidation of the organic-metallic compound. Ingress of MBTC vapor into the inside of the container is prevented by using a protective hood over the neck of the vials or bottles during the process that applies a back pressure.

The hot treatment has the following characteristics:

- Thickness from 20–80 coating thickness units (CTU), approximately 3–11 µg/cm^2 (120–200 Å) of tin dioxide over the side wall, the area most exposed to the friction with other containers
- Thickness from <10 CTU at the level of the neck finish, which is not exposed to abrasion with other vials or bottles

Cold treatment: The cold treatment is performed on vials and bottles after they exit the annealing lehr, by spraying a liquid solution between rows of bottles in order to avoid contamination inside the bottles. The solution used is macrogol stearate which is a mixture of monoesters and diesters of mainly stearic acid and/or palmitic acid. As this solution is soluble by water, there is no excess solution present after washing..1S (*USP41*)

In summary, the key factors that influence glass surface durability of containers manufactured from Type I glass are primarily the manufacturing conditions, such as the forming temperature, the time of exposure to heat, and the annealing conditions. The temperatures used for subsequent steps are lower than those used for forming and annealing (see *Table 2*), and do not pose an additional risk to the chemical durability of the glass from phase separation or volatilization. Post-manufacturing operations such as storage

in humid conditions and processing, such as depyrogenation in the presence of water vapor and terminal sterilization via autoclaving, can also impact glass surface chemical durability.

Table 2. Temperatures Encountered During Formation and Processing of ~~Type I Tubular~~. 1S (USP41) Glass Containers

Key Operations	Typical Temperatures (°)
Furnace	1500–1650
Sectioning of tube and base formation	1300–1500
Working range	1000–1250
Softening	750–850
Annealing	~~550~~ 530. 1S (USP41) –600
Depyrogenation range	250–350
Terminal sterilization	110–130

Change to read:

GLASS CONTAINER SOURCING

A pharmaceutical manufacturer has a range of choices when selecting a glass container for a drug product. These include the type of glass (I, II, or III), the production method (tubular or molded), surface treatments, as well as the size and neck finish of the container. It is important that the pharmaceutical manufacturers provide sufficient information on their requirements, such as the drug product formulation and the manufacturing and filling process, to allow the glass vendors to make informed judgments as to what containers to recommend.

Pharmaceutical manufacturers should consider the upstream provenance of the containers they purchase in that they should have sufficient knowledge of the glass manufacturing process and glass composition. This is essential to qualify a particular glass container type from a glass manufacturer for a particular drug product. The following knowledge is useful in this regard:

- Glass formulation
- ~~COE for Type I tubular glass (32–33 or 48–56 expansion)~~. Coefficient of thermal expansion of the glass (CTE). 1S (USP41)
- Whether the glass converter makes its own glass feedstock or sources the glass feedstock from a third party

- Manufacturing site for the glass containers; if multiple sites manufacture glass containers for a given product, information to determine if the glass containers made at the different sites will perform comparably
- Whether the glass surface has been modified through chemical treatment such as ammonium sulfate by the glass manufacturer or converter.

The maker and user of a glass container should collaborate to assure that glass quality is monitored and maintained throughout the extent of the glass supply relationship. Glass quality should also be monitored and inferred by the user through observations made during storage throughout the product's use-by-date. The glass manufacturer and glass user quality management programs should include the following:

- Quality audits of glass supplier (glass manufacturer and/or converter) by the glass user
- Establishing mutually agreed upon acceptable quality levels for lots of glass containers
- Monitoring and trending of the quality of glass batches, including but not necessarily limited to, monitoring the values obtained in *Containers—Glass ⟨660⟩, Specific Tests, Hydrolytic Resistance, Surface Glass Test*
- Monitoring and trending of glass quality and glass manufacturing process performance by the glass container manufacturer, including the effectiveness of methods used during the manufacturing process of the glass container to measure geometric tolerances and identify cosmetic defects
- Assurance that differences among different glass manufacturing sites do not significantly affect quality of a specified glass container sourced from multiple sites
- Presence of a system to monitor and qualify changes made to the glass manufacturing process and to inform customers of such changes.

Delete the following:

~~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 first reaction between the glass surface and an aqueous phase (water or water vapor) involves ion exchange~~

~~between hydrogen ions (or hydronium ions H_3O^+) from the aqueous phase and alkaline ions in the glass (*Equation 1*). This ion-exchange occurs in a short reaction time in acidic or neutral solutions. In basic solutions, the reaction occurs at the glass/water interface and dissolves the silica network. Further reaction of the silica releases silicic acid into the solution, thereby lowering the pH (*Equation 2*). These reactions result in hydration of the glass surface and an alkali-depleted, silica-rich layer.~~

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

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~~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 *Equations 4* and *5*.~~

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~~Reaction (*Equation 5*) increases the solubility of the silicic acid in solution, driving the reaction forward. At some point the limit of solubility is exceeded, and particles are formed via precipitation. 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..~~1S (*USP41*)

Change to read:

FACTORS THAT INFLUENCE INNER SURFACE DURABILITY

Glass Surface Chemistry

The following reactions apply only to the reaction of glass with water and give only an approximate scenario. The different glass compositions, the role

of converting/forming processes in modifying the near surface region, and the various components used in drug formulations (e.g., buffers, chelators, surfactants, tonicity modifiers, etc.) complicate the situation considerably. Numerous other reactions are possible based on the variables above; refer to the primary glass chemistry literature for additional information.

The initial reaction between the glass surface and an aqueous phase (water, water vapor or moisture) involves a surface hydration (*Equation 1*) followed by an ion exchange between hydrogen ions (or hydronium ions H_3O+) from the aqueous phase and the "available" alkaline and alkaline earth ions (sodium, potassium, magnesium, and calcium), not fully embedded into the glass silica network (*Equation 2*).

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When this ion exchange shown in *Equation 2* occurs in neutral or slightly acidic or slightly basic solutions, there is a slow rise in pH due to depletion of hydrogen/hydronium ions from the solution. When this ion exchange occurs in acidic solutions, only the available surface and near surface region alkaline ions are exchanged (*Equation 3*) then the reaction slows down due to the insolubility of silica in acidic solutions and the increasing diffusion distance required for ion exchange from the near surface region. In this case pH is not expected to change significantly and the surface becomes alkali depleted.

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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 4*. Dissolution occurs by the hydrolysis of the silicon-oxygen-silicon (Si–O–Si) bridging oxygen bonds and the pH can increase due to the release of more and more available alkaline ions, previously embedded in the network. Hydroxide ion (*Equation 4*) increases the solubility of the silicic acid in solution, driving the reaction forward.

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The silica-gel layer formed on the surface has different mechanical properties from those of bulk glass. Repeated hydration and dehydration of the layer leads to the cracking of the gel layer and eventual generation of subvisible or visible particles generally as flakes. This process is worsened as the gel layer increases in thickness. This phenomenon is well known in glass exposed for years to ambient moisture (known as weathering).

Glass Particles and Flakes

Glass particles observed in drug product solutions may be due to more than one cause and it is important to define their origin as well as differentiate these particles from glass flakes. An analysis of the composition of glass particles and flakes as well as their appearance can assist in establishing their root causes (*Table 3*).

Table 3. Source of Glass Particles and Flakes

Classification	Description	Composition	Source
Glass particles	Subvisible to visible	Composition of tubular glass	Sectioning of glass tube during manufacturing process
Glass particles	Subvisible to visible	Composition of glass	Abrasion of the outer surface of glass containers post formation
Inorganic glass-like particles	Subvisible	Silicon dioxide	Silicon dioxide leached from inner surface exceeding its solubility
Non-glass particles	Visible	Particles contain both glass elements and components of drug formulation, e.g., aluminum phosphate	Leached glass elements interacting with drug formulation to form complexes of limited solubility that precipitate
Glass flakes (lamellae)	Subvisible to visible flexible flakes (up to several hundred microns)	Alkali-depleted silica rich flakes	Delamination of interior surface

Glass Delamination

Glass delamination is a serious quality issue and can result in a product recall. The appearance of glass flakes is a lagging indicator of a strong interaction between the drug product and the inner surface of the glass. Although delamination is the most obvious visual indicator, it represents the final stage of a complex glass corrosion reaction, and can be observed only at a point where prevention is no longer an option. Adding further complexity to detection, mechanical energy from shaking or container-to-container contact during transportation may be required to dislodge the

flakes from the internal surface of a filled container and facilitate observation.

Tests for delamination combine the visual examination of the solution for the presence/absence of glass flakes, examination of the container's internal surface for the extent of chemical attack, and determination of the amount/ratio of leached glass elements to confirm the extent of chemical attack and identify the chemical attack mechanism (homogenous dissolution, non-homogenous dissolution, or in-between). Use of an aggressive test solution is appropriate to verify that the glass delamination assessment methods have the necessary sensitivity to confirm glass delamination. Use of the drug product solution at normal and/or accelerated conditions is required to assess suitability of the container/drug product formulation with respect to glass delamination. These examinations and the use of an aggressive test solution are intended to be conducted by the pharmaceutical manufacturer, not the glass manufacturer or converter..1S (*USP41*)

A number of factors have the potential to negatively influence the chemical 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 4*). Not only can an aggressive drug substance corrode the inner surface, but excipients such as buffers, chelating agents, organic acids, and high pH can also have a deleterious effect. For example, neutral solutions of sodium citrate attack glass with a severity similar to that of substantially alkaline solutions. Organic acids, such as gluconic and malonic acids, also corrode glass through a proposed mechanism of an ion exchange reaction in which metal ions on the glass surface are replaced by hydrogen ions from the acid. Not all listed factors negatively influence surface durability to the same degree, and can contribute to delamination either acting alone or in combination. 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. In some situations, the accumulation of risk factors may indicate that the selection of a glass container for a particular formulation should be done following a predictive screening study to establish more stringent glass quality requirements or may indicate that a glass container should not be used for a formulation.

Table 4. Factors That Influence the Inner Surface Durability of Glass Containers.1S (*USP41*)

Container Manufacture	Container Processing and Storage	Drug Product: Formulation, Processing, and Storage

Container Manufacture	Container Processing and Storage	Drug Product: Formulation, Processing, and Storage
• Glass composition • Molded or tubular container • Tubular manufacturing process: — Converting speed — Converting temperature	• Post-formation treatments: — Annealing.1S (*USP41*) — Ammonium sulfate — Washing — Depyrogenation • Storage and transportation.1S (*USP41*) conditions: — ~~High~~ Temperature and high.1S (*USP41*) humidity variation.1S (*USP41*)	• Drug substance • Formulation: — Acetate, citrate, phosphate buffers — Sodium salts of organic acids, e.g., gluconate, malate, succinate, tartrate, carbonate.1S (*USP41*) — High ionic strength, e.g., >0.1 M of alkaline salts — Complexing agents, e.g., EDTA — High pH, e.g., >8.0 • Terminal sterilization • Labeled storage conditions (refrigerated or controlled room temperature) • Shelf life

Change to read:

EVALUATION OF THE INNER SURFACE DURABILITY

Each lot of Type I, II, or III glass containers received by a pharmaceutical manufacturer must comply with a combination of .1S (*USP41*) the *Containers—Glass ⟨660⟩, Specific Tests, Hydrolytic Resistance, Surface Glass Test*, the *Glass Grains Test*,.1S (*USP41*) and the *Surface Etching Test*. A critical element of the *Surface Glass Test* procedure is the loading of the autoclave.

Critical Parameters in the Autoclave Loading Procedure

There are a number of practical details that will affect the ability to attain the required heating and cooling parameters and these are provided here to augment the instructions in *Containers—Glass ⟨660⟩, Autoclaving procedure*.

Possible variations within the method:

- Trays—design and materials of construction
- Autoclave loads—partial or full

- Sample types—single, e.g., all vials or mixed
- Sample sizes—single size or mixed sizes, e.g., 2-, 10-, and 50-mL vials

Trays

Samples may be held in trays or racks that are placed on the autoclave shelves. They provide a way of fitting samples snugly, preventing samples from falling over and optimizes to use of space. Trays can be fabricated from stainless steel (e.g., grade 316L), anodized aluminum or heat-resistant plastic materials. Not all materials used to make trays are excellent conductors of heat. For instance, the thermal conduction capacity of stainless steel is higher than that of plastic and this will impact the time duration of the autoclave cycle. Mixing trays of different materials and different sizes and designs will complicate the development of the required cycle.

Autoclave Loads

Loads may range from partial to full depending on the number and sizes of samples. The configuration of samples may also change with a partial load, depending on where the samples are placed on a single shelf or on multiple shelves.

Sample Types and Sizes

The simplest case would be a load of a single-sized container, e.g. all 10 mL vials. In many cases the load will consist of two or more container types with varying sizes. When there is a large range in container sizes in a single load (e.g., 2-, 10-, and 50-mL vials), this will affect the autoclave cycle. The contents of a 50-mL vial will take longer to reach the required temperature than the contents of a 2-mL vial. Thus if the cycle is set for the 2-mL vial, the extraction of the 50-mL vial will not reach the required time/temperature. Conversely, if the cycle is set for the 50-mL vial, the extraction of the 2-mL vial will be greater than the required time/temperature.

Autoclave Calibration and Load Mapping

The calibration of temperature and pressure should be carried out on a regular basis and at least once per year. Given the possible variations in load shown above, a single calibration run may not be suitable for all configurations. Loads that are similar in container sizes to those in the calibrated run may not require a separate calibrated cycle, but greater deviation in the load parameters may need a separate calibration.

Surface Glass Test.1S (*USP41*)

This test provides an indication of inner surface chemical durability but does not appear to provide a clear direct correlation with the propensity to form glass ~~particles~~ flakes.1S (*USP41*) or to delaminate. The alkalinity value represents the sum of all the internal surfaces of the container, and although this is representative for molded containers, tubular glass vials can have different degrees of surface chemical durability, depending on the location (e.g., just above the heel versus the side wall). A low surface alkalinity value can be obtained from containers treated with ammonium sulfate but the treatment itself may reduce the inner surface chemical durability, dependent upon the drug product formulation used to fill the ampule or.1S (*USP41*) vial. 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 chemical 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~~ Strategies.1S (*USP41*)

~~Screening methods help evaluate glass containers from different vendors (molded or tubular), glass formulations (e.g., 32–33 or 48–56 expansion for tubular glass), 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 looking only for glass lamellae, 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 techniques for evaluating the three key parameters are shown in *Table 3*.~~

~~Table 3. Analytical Techniques for Screening Studies~~

~~Parameter~~	~~Test Parameter~~	~~Instrumentation~~
~~Glass inner surface~~	~~• Degree of surface pitting~~ ~~• Chemical composition~~	~~• DIC Microscopy[a] or EM[b]~~ ~~• SIMS[c]~~

Parameter	Test Parameter	Instrumentation
	as a function of depth	
Extracted elements in solution	• Conductivity/pH • SiO_2 concentration	• Conductivity/pH meter • IC–MS[d] or ICP–OES[e]
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[f]

[a] Differential interference contrast microscopy.
[b] Electron microscopy.
[c] Secondary-ion mass spectrometry.
[d] Inductively coupled plasma–mass spectrometry.
[e] Inductively coupled plasma–optical emission spectrometry.
[f] Scanning electron microscopy–energy-dispersive X-ray spectroscopy.

Aggressive Screening Conditions .1S (USP41)

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 the suitability and sensitivity.1S (USP41) of the container without any specific reference test methods.1S (USP41) to a given compound. Such detect glass delamination. This.1S (USP41) testing can be helpful when for.1S (USP41) selecting a packaging system for which when.1S (USP41) the most chemically durable glass is desired. This testing also can be helpful in formulation is similar to the test solution and for.1S (USP41) determining if changes in glass quality have occurred or in assessing processing changes that have been made by the primary container manufacturer. *Table 5* provides three examples of model systems that could be used for this assessment. Other model systems may be developed by the end users.

Table 5. Formulations and Conditions Used to Accelerate Delamination

Formulation	0.9% Potassium Chloride pH 8.0	3% Sodium Citrate pH 8.0	20 mM Glycine pH 10.0
Conditions	1 h at 121° 1 or 2 cycles	24 h at 80°	24 h at 50°

Screening methods help evaluate glass containers from different vendors glass formulations 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 flakes. 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 flakes in solution. Taken together, these elements are assessed by predictive tests for formation of glass flakes and delamination, processes that reflect reduced durability. Predictive tests should look for precursors that lead to delamination rather than looking only for glass lamellae, 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 techniques for evaluating the three key attributes are shown in *Table 6*.

Table 6. Analytical Techniques for Screening Studies

Attribute	Test Parameter	Instrumentation
Glass inner surface	• Surface morphology (e.g., porosity, depth of reaction zones)	• DIC microscopy[a] or EM[b]
	• Chemical composition as a function of depth—appearance of the glass wall, e.g. shimmering, scattering, deposits	• SIMS[c]
Extracted elements in solution	• Conductivity/pH	• Conductivity/pH meter or ICP–OES[d]
	• Silicone/Barium/Aluminum/Sodium/Potassium/Calcium concentrations—concentration of glass elements and ratios	• ICP–MS[e]
Lamellae and visible and subvisible glass particles	• Presence of flakes	• Visual inspection
	• Flakes or particle number and size	• Particle-size analyzer
	• Flakes or particle morphology and composition	• SEM–EDX[f]

Attribute	Test Parameter	Instrumentation

[a] Differential interference contrast microscopy.
[b] Electron microscopy.
[c] Secondary ion mass spectrometry.
[d] Inductively coupled plasma–optical emission spectrometry.
[e] Inductively coupled plasma–mass spectrometry.
[f] Scanning electron microscopy–energy-dispersive X-ray spectrometry.

Predictive glass delamination studies should be designed to distinguish between general glass attack effects and specific features that are typical for a delamination process. In the best case, early indicators for delamination can be identified to support a risk assessment. Glass delamination is confirmed if glass lamellae are detected by visual inspection and chemically confirmed by chemical analysis or if delaminated regions are found on the inner glass surface. Early indicators/pre-delamination features are the appearance of reaction zones on the inner vial surface and significant changes in leached glass elements with glass element ratios changing significantly from the bulk glass. The first stage of chemical attack is indicated by the appearance of inner surface micro-roughness as evidenced by surface SEM analysis. Other features found include the appearance of shallow pits, bumps, holes, and deposits that have as their origin the manufacturing/processing of glass containers. The inner surface of the glass containers should be evaluated at the heel, mid-body, and for highly filled or inverted storage solutions, at the shoulder region, to help determine if the root cause for chemical attack is the manufacturing process of the containers (attack at the heel and/or shoulder) or a glass chemistry/drug product incompatibility (attack at the mid-body region)..▪1S (*USP41*)

~~**Screening Strategy for Drug Products**~~

~~Indicators include the appearance of a pitted, fractured inner surface particularly around the heel of the vial instead of a smooth surface, as well as a number of changes in the test solution, especially increases in SiO_2 concentration, the number of subvisible particulates in the solution, and a change in pH.~~

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▪1S (*USP41*)

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 5* 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 the appropriate accelerated conditions are 30°, then testing should occur at 30°. Many products or formulations cannot withstand the elevated temperatures or high

pH shown in *Table 5*. In addition, false positive testing results could be obtained because the unusually high temperatures shown in *Table 5* 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 7* shows some of the conditions that could be used for testing with a specific product.

Table 7. Screening Strategy for Glass Vials

Stress Test	Water Control	Drug Product Control
• Vials: washed, depyrogenated • Filled with stress test solution • Accelerated time and temperature treatment conditions	• Vials: washed, depyrogenated • Filled with *Water for Injection* • Autoclave if applicable to drug product • Accelerated drug product stability storage conditions	• Vials: washed, depyrogenated • Filled with drug product • Autoclave if applicable • Accelerated drug product stability storage conditions

Change to read:

~~CONCLUSIONS~~ SUMMARY. 1S (*USP41*)

Evaluation of the internal surface of glass containers begins with *Containers—Glass ⟨660⟩, Specific Tests, Hydrolytic Resistance, Surface Glass Test*, which uses water as the extracting medium. A low value is not always an indicator of a durable inner surface if the results are obtained using surface treatments (e.g., ammonium sulfate). Such treatments can lead to a silica-rich inner 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 high pH. The screening methods and strategies described in this chapter can assist in the evaluation of glass containers from different suppliers or on a lot-to-lot basis 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 4* should undergo particular scrutiny.