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30 November 2024

Desmond G. Hunt, Principal Scientific Liaison
12601 Twinbrook Parkway
Rockville, MD 20852

Reference: *USP Chapter <1660> Evaluation of the Inner Surface Durability of Glass Containers*

Dear Sir,

PDA appreciates the opportunity to provide feedback to the USP Packaging and Distribution Expert Committee on the proposed revision to *Chapter <1660> Evaluation of the Inner Surface Durability of Glass Containers*. In our attached comments, PDA offers specific comments and feedback that we believe will be helpful in the further development of this important chapter.

PDA is a non-profit international professional association of more than 10,000 individual members who are industry professionals having an interest in fields of pharmaceuticals, biological, device manufacturing, and quality. Our comments have been prepared by a committee of PDA members with expertise in the areas covered in this chapter on behalf of PDA's Scientific Advisory Board.

If you have any questions, please do not hesitate to contact me via email at wright@pda.org.

Sincerely,

Glenn E. Wright
President and CEO

CC: Jessie Lindner, PDA

PDA (Parenteral Drug Association®) Comments to USP General Chapter <1660>: Evaluation of the Inner Surface Durability of Glass Containers

General Comments

Comment(s)
PDA agrees with the general expanded scope and information of USP <1660> and feels the information is insightful and helpful to the end user. PDA recommends updating the scope so that the phrasing emphasizes the value of evaluation of the inner surface durability, verses the glass container manufacturing information. Additionally, it is recommended to update the language clarifying for readers that this Chapter is primarily intended for drug product manufactures, since stability is a product specific requirement.
The proposed revisions to USP <1660> appears to have adopted an expanded definition of the term "durability" to include mechanical reliability. For example, the entirety of Section 6 (Factors that influence container durability during filling operations) deals with glass handling-related topics that can introduce strength-limiting defects into containers. While this is generally useful information, a discussion of these topics is beyond what should be the intended scope of this guidance document. It is recommended that the proposed revisions to USP <1660> be written in a way that solely focuses on inner surface durability within the context of chemical stability – e.g., methods for evaluating hydrolytic resistance, glass delamination risk, etc. Implementing this recommendation would clarify the intent of the guidance, thereby improving its overall usability for the end user of the document.

SECTION 3. GLASS COMPOSITION

Table 1. General Range of Chemical Composition and Coefficient of Mean Linear Thermal Expansion for Quarts, Borosilicate, Aluminosilicate, and Soda-Lime-Silica Glass

Page Number	Reference Text	Proposed Change	Rationale
Pg 7-8	Table 1. General Range of Chemical Composition and Coefficient of Mean Linear Thermal Expansion for Quartz	PDA proposes updating Table 1. *See below for Table 1 proposal.	Table 1 does not include all borosilicate and soda-lime-silica glass types currently used in the market. In addition, coloring agents are not considered as a significant proportion of amber glass composition.

			The new proposal for Table 1: • Is aligned with the revised decision tree submitted by PDA in comments regarding the update of USP <660> • Covers the glass compositions currently used in the market • Eliminates some incorrect ranges and adds ranges where appropriate • Provides a comprehensive overview of composition ranges as well as important physical and chemical properties relevant for the use of glass as primary packaging material • Demonstrates also the differences between the ‘sub-families’ of the respective glass types, e.g. differentiation tubular and molded

* Table 1 General Range of Chemical Composition and Coefficient of Mean Linear Thermal Expansion for Quarts, Borosilicate, Aluminosilicate, and Soda-Lime-Silica Glass Proposal:

Glass Families / Identity	**Composition (Approx. Weight %)**							
	Fused Quartz Tubular	High Borosilicate "Tubular 33"	Medium Borosilicate "Tubular 51"	Borosilicate Moulded	Alumino -silicate Tubular	Low Borosilicate "Tubular 70"	Soda Lime Silicate Tubular	Soda Lime Silicate Moulded
Network Former **SiO_2**	>99.9	80 - 82	65 - 75	65 - 70	68 - 80	70 - 74	60-70	69-75
Network Former **B_2O_3**	-	≥ 12	≥ 8	9-13	-	≥ 5	< 6	0-1
Network Intermediates **Al_2O_3**	-	2	5-9	3-7	8-12	4-7	< 8	0.5-4
Sum Network Former/Intermediates	*99*	*97-92*	*92-78*	90-77	*92-76*	*86-79*	*84-74*	*80-69*
Type - Surface test - no interior processing, coating, treatment	Type I	Type I Converting Influences	Type I Converting Influences	Type I	Type I Converting Influences	Type I or III Converting Influences	Type III Converting Influences	Type III
Type - Surface test - interior processing, coating, treatment	Type I Limit I/II	Type I Limit I/II	Type I Limit I/II	Type I Limit I/II	Type I Limit I/II	Type I Limit I/II or Type III	Type II Limit I/II or Type III	Type II Limit I/II or Type III
Fluxes, Sum of Alkali Metal Oxides (**Na_2O, K_2O**)	-	3-5	6-9	8-11	8-15	10-14	12-17	12-16
Property Modifiers, Sum of Alkaline Earth Oxides (**MgO, CaO, BaO**)	-	0 - 1	0.5 - 2	2-4	3-10	4-9	1-12	10-15
Sum of Alkali Metal and Alkaline Earth	*0*	*3-6*	*6-11*	10-15	*11-20*	*14-23*	13-29	*22-31*
Type - Glass Grains	NA - Identity Req	Type I	Type I	Type I	NA - Identity Req	Type I or III	Type III	Type III
Testing	Surface Test & Identity							
Spectral Transmission - Amber	NA	NA	Yes – Amber Type I	Yes – Amber Type *I*	NA	Yes - Amber Type I or III	Yes - Amber Type III	Yes - Amber Type III
Extractables	NA- Identity Required	ICH-Q3D & USP 1160						
CTE (10^{-7}/K)	5.5	32 - 33	48 - 54	58 - 65	60 - 70	60 - 70	70-95	71-93
Fining Agents	No	Varies by Manufacturer (Cl, F, As, Sn, Fe, Sb, S, Ce)						

SECTION 4.0 FORMATION AND PROCESSING OF MOULDED AND TUBULAR GLASS CONTAINERS

Page Number	Reference Text	Proposed Change	Rationale
Pg 8	"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."	PDA proposes to remove the statement.	It is not clear why this statement is needed in a guidance chapter on evaluating inner glass surface durability. By removing text, it could help limit reader confusion.
Pg 8	"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."	PDA recommends updating the statement to: "Glass tubes of a specific diameter **and wall thickness** are formed from a stream of molten glass that exits the furnace, is cooled, and is sectioned into standard lengths."	By incorporating this minor change, it will make the description more complete and aid in reader understanding.
Pg 8	"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."	PDA proposes updating the statement to: "Gas flames are used to soften tubing glass to form the **flange**, neck, **and shoulder regions** to melt the glass to form the base of ampules or vials, and to separate the container from the glass tube."	By incorporating this minor change, it will make the description more complete and aid in reader understanding.
Pg 8	"Under certain time-temperature conditions, the glass can phase separate during forming, creating	PDA suggests removing this statement.	Phase separation has not been linked to inner surface chemical heterogeneity which is the scope of this Chapter. Would suggest removing statement to avoid reader confusion because

	nonhomogeneous surface chemistry on the interior of the bottom of the container."		content is not relevant to scope and could lead to reader confusion.
Pg 8	"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."	PDA recommends removing reference to phase separation: "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 volatilization."	Phase separation has not been linked to inner surface chemical heterogeneity which is the scope of this Chapter. Would suggest removing statement to avoid reader confusion because content is not relevant to scope and could lead to reader confusion.

SECTION 4.1 Container Treatments

Page Number	Reference Text	Proposed Change	Rationale
Pg 9	"If the glass breaks, it does so with an explosive character, with the size of the glass fragments produced decreasing as the localized tensile stresses in the glass increase (1)."	PDA recommends removing this statement.	This Chapter concerns methods for evaluating inner surface durability. Information on chemical strengthening to increase breakage resistance seems like it is out of scope for this Chapter and could lead to reader confusion.
Pg 9	"Although removing sodium ions from the surface reduces the propensity for pH shift, the treatment also removes structural elements, leaving a thin silica-rich inner surface layer."	PDA recommends updating the statement to the following: "Although removing sodium ions from the surface reduces the propensity for pH shift, **in the case of tubular vials**, the treatment also removes structural elements, leaving a thin silica-rich inner surface layer."	The statement only applies to tubular vials, not molded. Molded composition is uniform for bottom and side wall, which is not the case for tubular vials. For molded, ammonium sulfate treatment happens just after forming, at about 500°C-650°C. For tubular, the treatment happens inside annealing

			lehr, as tubular vials are not hot enough while ammonium sulfate introduced. By updating the statement as recommended, it improves technical accuracy and clarity for the reader.
Pg 10	“The hot treatment has the following characteristics: • Thickness of 20–80 coating thickness units (CTU), approximately 3–11 μg/cm2 (120–200 Å) of tin oxide over the side wall, which is the area most exposed to friction with other containers • Thickness of <10 CTU at the level of the neck finish, which is not exposed to abrasion with other vials or bottles”	PDA suggests updating and expanding the statement to the following: “The hot treatment has the following characteristics: • Thickness of 20–80 coating thickness units (CTU), approximately 3–11 μg/cm2 (120–200 Å) of tin oxide over the side wall, which is the area most exposed to friction with other containers • Thickness of <**20** CTU at the level of the neck finish, which is not exposed to abrasion with other vials or bottles. **An alternative treatment could be applied if the performance is equivalent or superior.”**	By making the change from <10 CTU to <20 CTU , this will take into account the specifications due to the detection limit of the equipment and the absence of zone between 10 and 20 CTU. The addition of the last statement allows for the possibility to use alternative hot treatments and aligns to the language used for the cold treatment recommendation.

SECTION 7.2 Glass Particles and Flakes

Table 3. Source of Glass particles and flakes

Page Number	Reference Text	Proposed Change	Rationale
Pg 13 - 16	Table 3. Source of Glass Particles and Flakes	PDA proposes updating formatting to horizonal or bullet format. *See below for Table 3 proposal.	The current layout for Table 3 is difficult to read because only 1-2 words are found per line and gaps exist between bulleted items. PDA's suggestion is to reformat table to allow more information to be viewable on one page to improve ease of reading.
Pg 16	• Sodalime is more susceptible than molded; molded is more susceptible than tubular on the basis of glass composition (i.e., alkali total weight percentage)"	PDA suggests removing statement from Table 3. *See below for Table 3 proposal.	Statement contains technical inaccuracies, (i.e., molded is not more susceptible than tubular glass). Removing statement would eliminate technical inaccuracy.

*Table 3. Source of Glass Particles and Flakes Proposal:

Classification	Mechanism	Description	Frequency	Location within container	Composition	Non-Exhaustive Examples	Corrective Action
Glass Particles	Glass breaks or fractures due to the application of stress	Subvisible to Visible	Sporadic	N/A	Composition of Container Glass	• Sectioning of glass tube during manufacturing process • Breakage of containers during filling/capping	• Work with glass manufacturer to improve sectioning process • Reduce line pressure • Ensure filling line tolerances are matched to container
Glass Particles	Abrasion from blunt frictive damage	Subvisible to Visible	Sporadic	N/A	Composition of Container Glass	• Glass to glass contact on filling lines • Glass to glass contact during transit	• Adjust filling line to reduce glass-to-glass and glass-to-metal contact • Adjust filling line • Adjust secondary packaging/shipment method/carrier
Precipitation of dissolved glass (Inorganic Insoluble Particle or Glass elements)	Glass elements leached from the container exceed solubility. Higher potential in alkaline pH solutions.	Subvisible to Visible	Consistent across all containers in lot	May be in solution and/or nucleated on container walls	Glass elements in ratios that differs from the composition of the container glass	• Hydrated silicate particles that can contain Al, Ba, Ca, Mg, etc. (e.g., $MgAl_xSi_yOH_z$ Temperature, time, high pH solutions, or other accelerated processing may affect solubility e.g. sterilization, 60C storage.)	• Work with glass manufacturer to test alternative glass compositions/coatings • Note: Inorganic insoluble particles can form with the Drug / API / Buffer only without interaction with the container.
Precipitation from container-drug interaction (Drug / API / Buffer with Container interaction)	Leached glass elements interact with drug formulation (buffer and/or API) to form complexes of limited solubility that precipitate. Note: This can	Subvisible (Haze low level – light scattering) Visible	Consistent across all containers in lot and between SKU's	May be suspended and/or nucleated on container walls	Particles contain both glass elements and components of the formulation	• Al-phosphate complex • Barium sulfate complex (e.g. Ba_2SO_4) • Iron Sucrose agglomeration	• Work with glass manufacturer to test alternative glass compositions/coatings • Changes needed to process or chemistry of Drug/API/Buffer

	occur with Drug/API/Buffer and any container closure component.						
Delaminated Glass flakes (lamellae) due to container near surface region chemistry changes in combination with drug formulation	Interaction of low durability changed durability near surface region of container with formulation, resulting in silica rich reaction zones that are eventually detached and released to solution	Subvisible to visible flexible flakes (up to several hundred microns)	Sporadic	Solution or surface, originates from the strongly heated container regions	Alkali-depleted silica rich flakes	• Phosphate buffered solutions • Carbonate buffered solutions • Solutions with salts • Any solution especially corrosive to low durability region (acid, base, or neutral). The rate of lamellae production is dependent on the rate of corrosion.	• Work with glass manufacturer on converting conditions • Select glass containers with uniform surface chemistry
Glass flakes due to poor glass chemistry / drug formulation incompatibility	Interaction of near surface region of entire container surface in contact with formulation, resulting in silica rich reaction zones that are eventually detached and released into solution	Subvisible to visible flexible flakes (up to several hundred microns)	Uncommon for Pharmaceutical Glass	All liquid contact surface area equally prone.	Alkali-depleted silica rich flakes	• Aggressive formulations in combination with container glass chemistry (e.g., high pH above pH 11 are aggressive to high silica glasses, low pH below 4 are aggressive to soda-lime.)	• Work with glass manufacturer on alternative glass compositions/coatings or surface treatments

7.3 Glass Delamination

Table 4. Factors Influencing the Chemical Durability of the Inner Surface of Glass Containers

Page Number	Reference Text	Proposed Change	Rationale

<table>
<tr><td>Pg 17</td><td>“Container Processing and Storage
Post-formation treatments:
Annealing
Ammonium sulfate
Washing
Depyrogenation
Storage and transportation conditions
Temperature and high humidity variation”</td><td>PDA proposes to add a bullet point to the Container Processing and Storage column.

“Container Processing and Storage
Post-formation treatments:
Annealing
Ammonium sulfate
Washing
Depyrogenation
Storage and transportation conditions
Temperature and high humidity variation
Ion exchange treatment”</td><td>Due to the implementation of ion-exchange surface treatment in general, this method should also be included here to aid in reader understanding.</td></tr>
<tr><td>Pg 17</td><td>“Drug Product Formulation, Processing, and Storage
Drug substance
Formulations:
Acetate, citrate, phosphate buffers
Sodium salts of organic acids (e.g., gluconate, malate, succinate, tartrate, carbonate)
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”</td><td>PDA proposes to add a bullet point to Drug Product Formulation, Processing, and Storage column.

“Drug Product Formulation, Processing, and Storage
Drug substance
Formulations:
Acetate, citrate, phosphate buffers
Sodium salts of organic acids (e.g., gluconate, malate, succinate, tartrate, carbonate)
High ionic strength (e.g., >0.1 M of alkaline salts
Complexing agents (e.g., EDTA)
High pH (e.g., >8.0)
Terminal sterilization</td><td>The added bullet point clarifies the potential importance of fill volume. The surface area to volume ratio is a generally important factor in glass corrosion, especially in low fill applications.</td></tr>
</table>

		• Labeled storage conditions (refrigerated or controlled room temperature) • Shelf life • **Ratio of container surface area to drug product fill volume”**	

SECTION 8.1 Critical Parameters in the Autoclave Procedure

Page Number	Reference Text	Proposed Change	Rationale
Pg 17	“Figure 1. A summary of factors that influence titration results including indications of their criticality and the difficulty of controlling them.”	PDA proposes to relocate Figure 1 to Section 8.3 Surface Glass Test.	Figure 1 contains information that is pertinent to the material in section 8.3. By relocating the Figure, it will aid in reader understanding.
Pg 18	“The calibration (qualification and validation) of temperature and pressure should be carried out on a regular basis, at least once per year.”	PDA recommends updating statement as follows: “The calibration (qualification and validation) of temperature and pressure should be carried out on a regular basis, **as appropriate based on risk assessment**.”	Updating the statement as recommended, will align the Chapter’s recommendations with those demonstrated by *ISO 15378:2015 Primary Packaging Materials for Medicinal Products - Particular Requirements for the Application of ISO 9001:2008, With Reference to Good Manufacturing Practice (GMP*) that comprehensive re-validation (e.g., every 5-10 years) is sufficient if other actions and premeasures are involved in standard testing (e.g., control cards, inclusion of reference/standard sample for each measurement, etc.). A re-validation plan should exist based upon a risk-based validation strategy.

			By allowing firms to base the frequency of calibration on risk-based analysis, firms will be given the flexibility to arrive at different outcomes for each laboratory, depending on site specific factors and quality risk management (QRM) requirements.

8.2 Critical Parameters in the Heating Cycle Procedure

Page Number	Reference Text	Proposed Change	Rationale
Pg 18	"Titration Variations in titration can be reduced by using automatic titrators. To increase the reproducibility of the titration results, personnel should be well-trained. Observation of the color change is subjective and should be facilitated by using standard conditions, such as the same set of lighting and background color conditions. Also, the angle of observation should be kept constant, and if possible, the impact of daylight should be controlled. As the glass burettes can produce relatively big droplets, the burette tips can be considered to be connected to a micropipette to obtain smaller and more controllable droplets."	PDA recommends relocating content to Section 8.3 Surface Glass Test.	Titration is not included in the heating cycle procedure of autoclave but after this step. This content would be better suited to be relocated in the 8.3 Surface Glass Test section.
Pg 18	"As the glass burrettes can produce relatively big droplets, the burrette tips	PDA proposes to update the statement as follows:	As currently written, the sentence could be misinterpreted to mean that

	can be considered to be connected to a micropipette to obtain smaller and more controllable droplets.”	“As the glass burrettes can produce relatively big droplets, **consider use of more dilute titrants, or burrettes (e.g. micropipette) which can produce** smaller and more controllable drops.”	one is putting a glass burrette tip on a micropipetter. The tip (size and material) drives the drop size, not the pipette. By updating the statement as proposed, the reader is provided considerations that should be addressed during method validation.

8.3 Surface Glass Test

Page Number	Referenced Text	Proposed Change	Rationale
Pg 19	“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 flakes or to delaminate.”	PDA suggests updating the statement to the following: “This test provides an indication of inner surface chemical durability but does not **necessarily** provide a clear, direct correlation with the propensity to form glass flakes or to delaminate.”	As currently written, it seems to imply there is a lack of knowledge/information available regarding the test. By updating the statement it will clarify intent.

8.4 Predictive Screening Strategies

Page Number	Referenced Text	Proposed Change	Rationale
Pg 19	“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).”	PDA recommends updating the statement to the following: “A low value is not always an indicator of a durable inner surface if the results are obtained using surface treatments	The statement only applies to tubular vials, not molded. Molded composition is uniform for bottom and side wall, which is not the case for tubular vials.

		(e.g., ammonium sulfate), **in the case of tubular vials**."	For molded, ammonium sulfate treatment happens just after forming, at about 500°C-650°C. For tubular, the treatment happens inside annealing lehr, as tubular vials are not hot enough while ammonium sulfate introduced. By updating the statement as recommended, it improves technical accuracy and clarity for the reader.

9. EXTRACTABLE ELEMENTS

Table 9. Extraction Solutions and Conditions

Page Number	Referenced Text	Proposed Change	Rationale
Pg 21-22	"Temperature (^{0}) 121 ± 1"	PDA proposes to update Temperature recommendation for purified water in 60 min in autoclave. "Temperature (^{0}) **122** ± 1"	By making the proposed update to the temperature range to better align with autoclave parameters.

10. SPECTRAL TRANSMISSION

Page Number	Referenced Text	Proposed Change	Rationale
Pg 22	"Typically, iron and titanium are used in currently marketed amber borosilicate glass, and iron and manganese are used in amber soda-lime-silica glass."	PDA recommends updating the statement as follows:	Both iron and titanium or iron and manganese are used in amber borosilicate glass. Iron, sulfur and

		"Typically, iron and titanium **or iron and manganese** are used in currently marketed amber borosilicate glass, and iron, **sulfur, and carbon** are used in amber soda-lime-silica glass."	carbon are used for amber soda-lime-silica glass, not iron and manganese. The recommended update will make the statement technically accurate and will improve reader understanding.
Pg 22	"The wall thickness of tubular containers is relatively constant on the side wall. The wall thickness for a particular container type and size can be used to calculate spectral transmission."	PDA suggests the following: "The wall thickness **for a particular container type and size can be used to calculate spectral transmission**."	Historically, molded amber glass bottles and vials typically had minimum glass thicknesses which would align with a 10% maximum transmission. However, in recent years, driven by market requirements and sustainability initiatives, lighter weight molded vials are available which exceed the 10% threshold. Thus, a variable, or stepped scale for maximum transmission of amber, molded glass containers is also necessary.

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PDA submits comments to regulatory agencies and pharmacopeial bodies when draft guidance or legislation is issued for public comment. Members of the PDA community work together to provide feedback regarding the content to ensure a broad industry perspective is presented and considered for inclusion or revision of the draft document.

PDA Regulatory Commenting documents are consensus documents, prepared by member-driven teams (listed below) comprised of content experts, including scientists and engineers working in the pharmaceutical/biopharmaceutical industry, regulatory authorities and academia.

The final working draft is reviewed by the PDA Advisory Board(s) aligned to the PDA Commenting Effort subject matter. PDA's four Advisory Boards are classified as Science, Advanced Therapy Medicinal Products, Biopharmaceuticals, and Regulatory Affairs and Quality.

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