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30 November 2024

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

Reference: *USP Chapter <660> Containers-Glass*

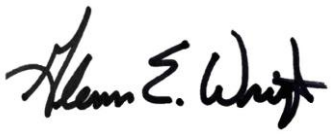
Dear Sir,

PDA appreciates the opportunity to provide feedback to the USP Packaging and Distribution Expert Committee on the proposed revision to *Chapter <660> Containers-Glass*. 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 <660>: Containers-Glass

General Comments

Comments
PDA recommends modifying the Chapter title to "*Glass Packaging Components and Their Composition* <660>" for clarity and conciseness. This USP Chapter applies for both users in the Pharmaceutical and Bio-Tech industry. The Bio-Tech industry clearly differentiates between "packaging systems" and "packaging components", and between "materials of construction" and "material composition". By making this modification to the Chapter title, it would be more accurate, and representative of the terminology used across the industry as a whole. This modification would also align the Chapter title with the definitions provided in USP <659>. Additionally, it is recommended to add cross-references to USP <659> when these harmonized terms are used in the text of the Chapter.
PDA proposes modifying the Introduction to better align with the content of the Chapter. The primary, and important value of this Chapter, is to set a baseline of performance standards for glass packaging components, once glass is the chosen packaging to be used. Chapter <660> deals only with one element of a packaging system – Glass Packaging Components; and with only one material of construction – Glass. As currently written, other materials of construction for packaging systems seem to be included in the scope of this guidance. This would include rubber (many various formulations), rigid plastics (many various formulations), flexible bag materials, aluminum, etc. Other than citing cross-references to other chapters containing related information, repeating or explaining content of other Chapters, will confuse users of this Chapter. By modifying the wording as proposed, it would clarify for the reader the intended applicability of this guidance.
PDA recommends updating the scope to clarify the intended implication of this Chapter. The current statement leaves room for interpretation by implying there are other glass packaging components to be considered, without elaboration. The tests and protocols of this Chapter should not be applied to glass packaging formats which have not been qualified as bracketed by this Chapter's standards. The performance criteria of the Chapter are very specific to format and container attributes, and the scope statement should reflect this. The proposed update would remove this ambiguity and provide clarification to the reader regarding what test should be applied to what surfaces at what time. Additionally, PDA recommends moving away from the use of "flint", as this term is a commonly used misnomer for clear glass, but at a technical level is non-pharma glass.

SECTION 3. DESCRIPTION

Page Number	Reference Text	Proposed Change	Rationale

Pg 9	The inner surface of glass containers may be treated to improve hydrolytic resistance or water repellency. The outer surface of glass containers may be treated to reduce friction for protection against abrasion or breakage. The outer surface treatment is such that it does not contaminate the inner surface of the container. For additional information on inner and outer surface treatments of glass containers, see Glass *Containers Used in Pharmaceutical Packaging/Delivery Systems-Manufacture and Evaluation of the Inner* Surface *Durability* (1660).	PDA recommends modifying the text to: "The inner surface of glass containers may be treated, **coated, or otherwise modified** to improve hydrolytic resistance. The outer surface of glass containers may be treated to reduce friction for protection against abrasion or breakage **provided the** outer surface treatment is such that it does not contaminate the inner surface of the container. For additional information see *Glass Containers Used in Pharmaceutical Packaging/Delivery Systems–Manufacture and Evaluation of the Inner Surface Durability (1660).*"	By making the proposed update, the statement will encompass the other treatments discussed in Chapter <1660>. Additionally, the use of the term "water repellency" is not clear and could lead to confusion.

SECTION 4: SPECFIC TESTS

Page Number	Reference Text	Proposed Change	Rationale
Pgs 9-10	Section 4. Specific Tests Glass Grains Test	PDA proposes to retain legacy glass grains test method with introduction of alternative methods – WD-XRF, ICP, Wet Chemistry for Identity.	By retaining the glass grains test and introducing alternative methods, this will allow for more inclusive identification test options. There is a large, existing base of drug products packaged in glass containers, from small volume parenteral containers produced from tubing glass compositions to products in molded glass, particularly for large volume parenterals (LVPs), as well as tubular glass containers used in

			non-parenteral applications. Typically, all these containers must be certified to both USP <660> and EP 3.2.1. As currently proposed, the revision will likely create hardship for these glass and pharmaceutical manufacturers due to cost and lack of availability for WDXRF technology in many incoming test labs. It will also increase risk of lower performance Type III glass containers. The glass grains test not only differentiates between borosilicate and soda-lime-silicate glasses, but it also sets a minimum performance standard regarding alkaline extraction of the bulk glass. The proposed WDXRF method only allows identification of compositional differences; while providing no minimum bulk glass performance standard. There is a strong likelihood that removal of existing tests will create significant burden, and possible disruption to the supply line of legacy products, which represent hundreds of millions of patient doses. For the large,

			existing base of use, the Chapter should maintain the requirements and methods currently harmonized USP/EP testing to differentiate the two legacy compositions, while adding as options the use of the new identification methods where appropriate.
Pgs 9-10	Section 4. Specific Tests	PDA recommends to not expand the extractable test for the element aluminum.	The inclusion of a new test should improve the overall effectiveness of the compendial guidance. Especially for glass types which are in use since decades (borosilicate and soda-lime-silica glass) an increased measurement effort should be justified e.g. for safeguarding patient safety. Aluminum itself is of low inherent toxicity as outlined in the ICH Q3D and therefore ranked in class 'other elements' and considered in E&L studies anyway (also see USP <232>). For specific therapy fields, an Al limit is scientifically necessary with regards to patient safety, yet the corresponding regulations already exist, such as 21 CFR 201.32 - "Aluminum and large and small volume parenterals used in total parenteral

			nutrition. In addition, the proposed limit seems to be arbitrarily as well as the fact, that the extraction level after the described stress method is of low predictive ability for the final drug formulation - both making it difficult to assess the appropriateness of the recommendation. The performance of the alumina testing in the lab exhibits significant uncertainty at these low levels – also among high-quality glass laboratories. This was demonstrated in a round robin test and two publications (see Guglielmi et al., Appl. Glass Science, 2020 and Guglielmi et al., PDA J Pharm Sci and Tech, 2018, 72, 553-565): 'Only the values for SiO_2 and B_2O_3 will be considered, as the data for Al_2O_3 are highly dispersed due to the very low concentration of aluminum ions in solution and the low sensitivity in ICP-OES for this element.' (eg. range of aluminum oxide values of same batch by different laboratories: 0.17 – 1.14 ppm).

			For a main component of a glass composition, a single limit applying for all container sizes and types doesn't respect the mathematical background of surface/volume ratio for a concentration-based limit. Also see Biavati et al. (2010) for a nice example of how aluminum extraction can scale as a function of surface area-to-volume ratio with water extraction (factor of 10: 0.02 µg/ml for 100 ml vs. 0.2 µg/ml for 10 ml). To container size – comparable to the table of limits of the inner surface test (table 4) – should be integrated with the limits determined by accompanied studies for their justification. However, to reduce complexity, one could also think about only one differentiation level (e.g. Containers > 5ml: 1.0 µg/ml, Containers ≤ 5ml: 2.0 µg/ml).

SECTION 4: SPECFIC TESTS

Table 2. Elemental Composition and Performance Tests According to Glass Composition

Page Number	Reference Text	Proposed Change	Rationale

Pgs 9-10	"a Aluminosilicate amber glass is not currently available. b Dealkalization can be performed on borosilicate glass but is not recommended (see <1660> 4.1 Container Treatments)"	PDA proposes removing footnote A and updating footnote B in Table 2. Proposed wording for footnote B: "b Dealkalization can be performed on borosilicate glass but is not recommended **for tubular vials**."	To reduce confusion, non-existing products should not be referenced and therefore it is recommended that footnote A be removed. Would move away from saying "not recommended" as blanket statement and provide clarification that in the case of tubular vials dealkalization is not recommended. Dealkalization can be performed on molded glass and some registered drug products require this to be performed, making current statement not suitable. This change will also align <660> with the recommendations found in <1660>.
Pgs 9-10	Table 2. Elemental Composition and Performance Tests According to Glass Composition Inner Surface Treatments (4.3)	PDA proposes to remove the column "Inner Surface Treatments" from the table.	The content in Section 4.3 is out of scope regarding inner surface suitability assessment. Section 4.3 describes mechanical property testing which is only one of many physical property tests which become part of specifications and appear on supplier certifications of analysis. There is no performance standard defined, so there cannot be a performance test that is in scope for this Chapter.
Pgs 9-10	Table 2. Elemental Composition and Performance Tests According to Glass Composition	PDA suggests adding the following statement after Table 2: "**There are multiple compositions/treatment options which can satisfy the performance**	By providing this explanation to set documentation and communication best practice, it will allow reader to better understand the information in table/guidance.

		criteria of the described Glass Types. Suppliers and users of glass containers should clarify composition in specifications and certificates of conformance/analysis. Certificates of analysis need to specify the type compositional family [e.g., Type I (Aluminosilicate, Borosilicate, Quartz), Type II or Type III (Soda-lime-silicate)], and any treatment (where applicable) of the glass provided."	It would also be helpful to provide a range of composition for each type of glass to eliminate reader confusion.

SECTION 4.1: Elemental Composition by Wavelength Dispersive X-Ray Fluorescence (WDXRF)

Page Number	Reference Text	Proposed Change	Rationale
Pg 10	"Bulk glass composition may be determined by wavelength dispersive X-ray fluorescence spectrometer (WDXRF); see *X-Ray Fluorescence* Spectrometry <735>."	PDA suggests adding a statement clarifying when this test is needed. "Bulk glass composition may be determined by wavelength dispersive X-ray fluorescence spectrometer (WDXRF); see *X-Ray Fluorescence* Spectrometry <735>. **Test may be performed either on the canes used for the manufacture of tubular glass containers or on the containers.**"	By adding this statement, it clarifies that the test result and glass classification is already determined by the glass tubing supplier.
Pg 10	**"Apparatus:** WDXRF (see <735>). Use an X-ray fluorescence spectrometer with a minimum power of 3 kW and a mask size of either ≤32 mm or	PDA proposes updating the text to: **"Apparatus:** WDXRF (see <735>). Use an X-ray fluorescence spectrometer	The determination of the element boron via XRF bears a high measurement uncertainty. Thus, for an exact analysis, the determination of boron is recommended to be perfromed by a

	≥27 mm, capable of measuring boron. Note-For measurement of quartz glass, use a 6- or 10-mm mask."	with a minimum power of 3 kW and a mask size of either ≤32 mm or ≥27 mm, capable of measuring boron. **For more accurate results, a wet chemical analysis (reference to ISO21078-1: Determination of boron (III) oxide in refractory products Part 1: Determination of total boron (III) oxide in oxidic materials for ceramics, glass and glazes) can be performed.** Note-For measurement of quartz glass, use a 6- or 10-mm mask."	wet chemical digestion, as described in ISO21078-1. Using WDXRF methods only is restricticting the user to a limited dertermination method for boron.
Pg 10	"**Ancillary equipment for puck samples:** Use an oven and/or burner capable of achieving 1000° minimum; tools to contain and crush glass, such as a hammer or crushing tool, plastic bag, cloth, and paper; a fixture or carbon mold the size of mask; a grinder and polisher with polishing wheels (120 grit, 320 grit, polishing cloth) and a cerium oxide polishing agent."	PDA recommends modifying the text to: **"Ancillary equipment for puck samples:** Use an oven and/or burner capable of achieving 1000° minimum; tools to contain and crush glass, such as a hammer or crushing tool, plastic bag, cloth, and paper; a fixture or carbon mold the size of mask and a grinder and polisher with polishing wheels (120 grit, **at least 320 grit, polishing cloth) and a cerium oxide polishing agent to obtain a mirror surface**."	By updating this statement, it will clarify for the reader that the importance of the polishing step is to achieve a mirror surface on the glass. Achieving this mirror surface is important in the successful determination of the glass composition (i.e., improved accruracy, reduced noise, etc.).
Pg 10	**"Screening method for quartz glass:** Quartz glass may be identified by WDXRF using unpolished samples of the container wall. If the result is more than 98% silicon dioxide, the sample is identified as quartz glass. If the sample does not contain more than 98% silicon dioxide, the sample is formed into a	PDA recommends updating statement to align with Figure 1. **"Screening method for quartz glass:** Quartz glass may be identified by WDXRF using unpolished samples of the container wall. If the result is more than **or equal to** 98% silicon dioxide, the sample is identified as quartz glass.	The specification is not exact compared to Figure 1; the recommended update will harmonize the content.

	polished glass puck as described under *Manufacture of a glass puck*."	If the sample does not contain more than 98% silicon dioxide, the sample is formed into a polished glass puck as described under *Manufacture of a glass puck*."	
Pg 10-11	"**Polishing of glass puck or base sample:** Prepare a cerium oxide slurry using cerium oxide polishing compound and *Purified Water*. Use a polisher to polish the sample in steps with various polishing wheels (e.g., 120 grit, then 320 grit, and finally, a fine polishing cloth). Polish the sample for 3–5 min or as necessary to ensure a smooth mirror finish. If the sample does not have a mirror finish, repeat the polishing steps."	"**Polishing of glass puck or base sample:** Prepare a cerium oxide slurry using cerium oxide polishing compound and *Purified Water*. Use a polisher to polish the sample in steps with various polishing wheels **to ensure a smooth mirror finish.** If the sample does not have a mirror finish, repeat the polishing steps.	By updating this statement, it will clarify for the reader that the importance is to achieve a smooth mirror finish, regardless of what grit is used. Achieving this mirror surface is important in the successful determination of the glass composition (i.e., improved accruracy, reduced noise, etc.).
Pg 11	"**Method 1:** To screen for quartz glass, place a piece of the container wall in the sample holder of the WDXRF and measure silicon dioxide. If silicon dioxide is >98%, the sample is quartz."	PDA recommends updating statement to align with Figure 1. "**Method 1:** To screen for quartz glass, place a piece of the container wall in the sample holder of the WDXRF and measure silicon dioxide. If silicon dioxide is ≥98%, the sample is quartz."	The specification is not exact compared to Figure 1; the recommended update will harmonize the content.
Pg 11	Figure 1. Decision tree to determine glass compositional families	PDA recommends updating Figure 1. *See below for updated figure example.	The decision tree does not capture all glass compositions currently in use. For example, the glass compositions covered by the Section 3.3 expansion of borosilicate glass (e.g. Corning 33, Schott BORO-8330) and Type III amber glass (Nipro G38, Schott ILLAX).

			Also, the acceptance criteria for soda-lime silica glass are not representative of this glass type because it does not refer to the key oxides. Additionally, the decision tree is currently not aligned with Chapter <1660> Table 1. General Range of Chemical Composition and Coefficient of Mean Linear Thermal Expansion for Quartz, Borosilicate, Aluminosilicate, and Soda-Lime-Silica Glass. PDA has provided an updated figure for consideration that addresses these inconsistencies, and it can be found below. The figure is arranged by acceptance criteria (in % by weight) with the following composition ranges: 1. Quartz glass: Silicon dioxide is ≥98% 2. Borosilicate glass: Silicon dioxide is <98% and boron trioxide is ≥6% 3. Aluminosilicate glass: Silicon dioxide is <98%; boron trioxide is <6% and aluminum trioxide is ≥8% 4. Soda-lime-silica glass: Silicon dioxide is <98%; boron trioxide is <6%, aluminum trioxide is <8% and sum of sodium and calcium oxides is ≥12%

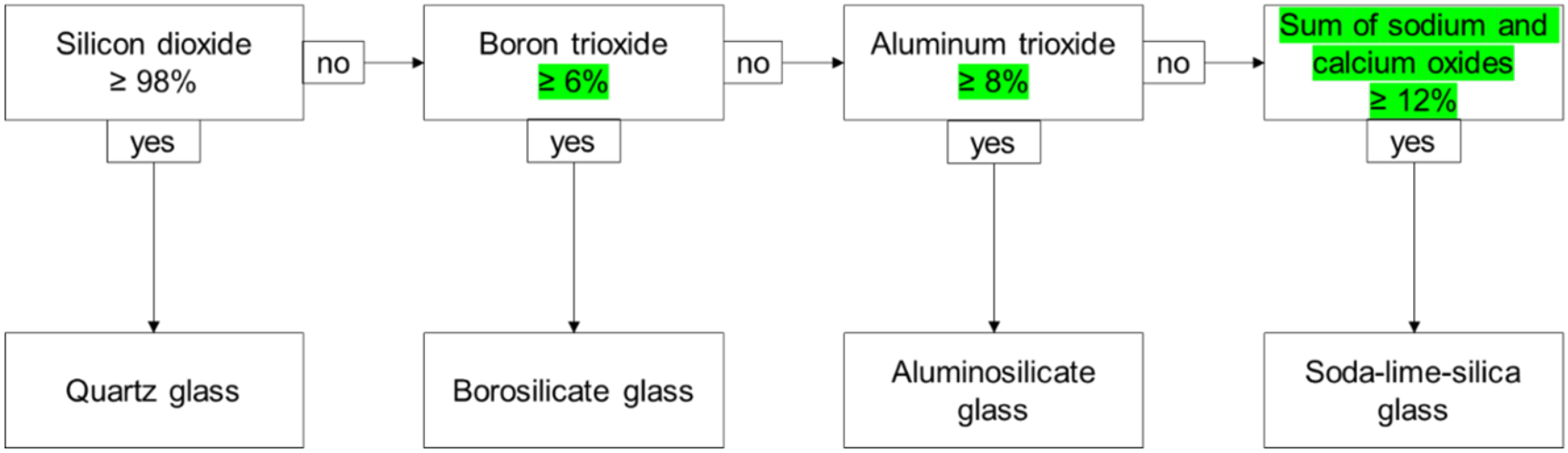


*Figure 1. Decision tree to determine glass compositional families

SECTION 4.2: Determination of Inner Surface Hydrolytic Resistance

Page Number	Reference Text	Proposed Change	Rationale
Pg 11	"Reference materials are available for both borosilicate glass (SRM 623) and soda lime silica glass (SRM 622) from the National Institute of Standards and Technology."	PDA proposes removing reference to SRM 623 from the Chapter. "Reference materials are available for soda–lime–silica glass (SRM 622) from the National Institute of Standards and Technology."	Standard 623 has been discontinued and is no longer produced. There are no alternatives according to the National Institute of Standards and Technology. Removal of this content would reduce reader confusion. Additionally, SRM 622 is only of benefit if the Glass Grains test is retained. As Chapter is currently written, Glass Grains test has been removed.

			The PDA also recommends consideration for the addition of quartz or aluminosilicate standards. As currently written, no information regarding reference materials for these glass types is provided.
Pg 12	**"Water:** *Purified Water,* or reagent grade water with a conductivity of not more than 5.0 µS/cm at 25° (not more than 4.3 µS/cm at 20°) may be used for cleaning the autoclave, conditioning unused glassware, determining the filling volume."	PDA proposes updating statement to align with ISO4802-1: 2023 water quality definition: **"Test water:** Prepare the test water from purified water by multiple distillations. Remove the carbon dioxide by boiling for at least 15 min before use in a boiling flask of fused silica or borosilicate glass, and cool."	'Purified water' has replaced 'carbon dioxide free water', yet the carbon dioxide content strongly influences the titration result. The current proposal would require a lower water quality than what was required previously. According to USP General Chapter, conductivity value of Purified Water is 1.3µS/cm at 25°C. If this statement is not changed, such a large difference in accepted conductivity value may give inaccurate results as concentration of ions increase, leading to increase in conductivity value and therefore may have an impact on the results of inner surface hydrolytic resistance. The proposed change would lead to more accurate results and decrease measurement uncertainty. In addition, the proposed change would be harmonized with *ISO4802-1:2023 Glassware — Hydrolytic resistance of the interior surfaces of glass containers Part 1: Determination by titration method and classification*.
Pg 12	"The resulting solution should be red. Not more than 0.1 mL of 0.02 M	PDA recommends adding the statement:	According to USP <1660>, color drives the control. Auto titrators are

	sodium hydroxide is required to change the color to yellow. A color change from red to yellow corresponds to a change in pH from pH 4.4 (red) to pH 6.0 (yellow)."	"**For accurate pH measurements, it is recommended that the user ensure methodology alignment with the supplier.**"	calibrated to use color, if they are following the standard. Using pH values alone could render a different result. By rewriting the statement, emphasis is placed on the color to aid in reader understanding. Additionally, regardless of what method is selected (i.e., auto titrator or titration wet chemistry), the supplier and user need to be aligned to ensure accurate measurements.
Pg 13	**"Cleaning:** Remove any debris or dust. Shortly before the test, rinse the containers twice with *Purified Water* and allow to drain. Complete the entire cleaning procedure-from the first rinse-within 20 ± 5 min. Sealed ampules may be warmed in a water bath or an air oven at about 40° for approximately 2 min before opening. This helps to avoid container pressure when opening. Do not rinse again before testing."	PDA proposes updating the statement to the following: **"Cleaning:** The following cleaning process for each container shall be completed within 20 min to 30 min. Remove from all open samples any debris or dust that has collected during storage and transport. Shortly before the test, fill each container to the brim with the purified water at ambient temperature and allow to stand for (20 ± 5) min. Immediately before testing, empty the samples, rinse twice with purified water, and then once with the test water and allow to drain. Closed ampoules shall not be rinsed before testing."	Standing time of the filled containers is not defined (as it has been in the previous version as well as in ISO standards), making the test more imprecise than before. The current proposal does not provide guidance as to how to conduct the procedure and leaves room for individual interpretation. By updating the cleaning requirement to that found in *ISO4802-1:2023 Glassware — Hydrolytic resistance of the interior surfaces of glass containers,* it will lead to more accurate results and decrease measurement uncertainty.

SECTION 4.2: Determination of Inner Surface Hydrolytic Resistance

TABLE 4. Limit Values for Inner Surface Hydrolytic Resistance Test

Page Number	Reference Text	Proposed Change	Rationale
Pg 14-15	Table 4. Limit Values for Inner Surface Hydrolytic Resistance Test	PDA proposes updating Table 4 to a simple performance table with a single Type I/II limit and a Type III limit, with notation for quartz. *See below for Table 4 proposal.	As currently presented, Table 4 addresses performance and identity as one characteristic, which could be confusing for the reader. Below, the table is reformatted so performance is the main header, and performance and identity are no longer combined. The proposed Table 4 has been restructured to have Type I and Type II combined and Type III as a separate column. Type II glass must share the same hydrolytic resistance limits as Type I, this is reflected in the proposal. The current table has hyphens for some Quartz Container values which could be confusing for readers. The proposed revised table has no hyphens and provides values for all Filling Volumes for Type I, II and II glass. However, a footnote has been added clarifying the background noise issues readers may experience due to test method limitations.
***Table 4. Limit Values for the Surface Glass Test**			

Filling Volume (mL)	Maximum Volume of 0.01 M HCl per 100 mL of Test Solution (mL)	
	Types I and II	Type III
Up to 0.5	3.0	30.0
0.5 to 1	2.0	20.0
1 to 2	1.8	17.6
2 to 3	1.6	16.1
3 to 5	1.3	13.2
5 to 10	1.0	10.2
10 to 20	0.80	8.1
20 to 50	0.60	6.1
50 to 100	0.50	4.8
100 to 200	0.40	3.8
200 to 500	0.30	2.9
Above 500	0.20	2.2

Note: Quartz containers, lacking any appreciable alkali and other non-silica additives, theoretically should achieve surface hydrolytic resistance results approaching zero. In practice, results are typically non-zero, with accuracy and variability in results reflective of the test method's limitations at the low end of the measurement range.

SECTION 4.3 Surface Treatments

Page Number	Reference Text	Proposed Change	Rationale
Pg 15-16	Section 4.3 Surface Treatments	PDA proposes to remove Section 4.3: Surface Treatments and include	Chapter <1660> already includes information regarding treatment

		reference to the ISO 8113 and ISO 11040-4 test for mechanical strength in <1660> as a characterization test for development. If the proposal to remove Section 4.3 is not plausible, suggestions for updating Section 4.3 content has been provided for consideration in the comments to Section 4.3 below.	purposes and methods (e.g. section 4.1). As written, Section 4.3 implies use of the test to only one process (ion-exchange K+ for Na+). This test is not usually performed by drug product manufacturers for incoming glass, nor are they equipped to do so. Receiving sites may determine that the incoming glass has been properly treated through identification testing. Additionally, as currently written the test varies from the ISO 8113 method and harmonization is suggested. Table 2 are required tests, however the acceptance criteria in 4.3 appears vague: "None of the treated samples exhibit visual signs of damage up to the value (kN or kg force/mm2) provided by the manufacturer for the size of the particular container, under either vertical or horizontal load."
Pg 15	"The process can also be applied to Type I performance borosilicate glass to reduce the propensity for pH shift. However, this is not generally recommended since it leaves a thin silica-rich inner surface layer. The inner surface hydrolytic resistance establishes the glass performance type."	PDA recommends the removal of Section 4.3. If not accepted, PDA proposes to update this statement as follows: "The process can also be applied to Type I performance borosilicate glass to reduce the propensity for pH shift. However, t**here are known risks to dealkanizing Type I borosilicate (see Chapter <1660> for additional information) and** this is not generally recommended **for tubular vials**, since	The process is not recommend for tubular vials but is allowable for molded vials. Moreover, in Chapter <1660> Section 4.1 Container Treatments, it is not indicated that this treatment is not recommended for Type I vials. This update will align the recommendations in the two Chapters and direct the reader to Chapter <1660> for additional clarifying information.

		it leaves a thin silica-rich inner surface layer. The inner surface hydrolytic resistance establishes the glass performance type."	
Pg 15	**"Data:** Record the number of samples, the test speed (millimeters per minute), and the peak force value achieved kN or kilograms of force per square millimeters (kg force/mm^2)."	PDA recommends the removal of Section 4.3. If not accepted, PDA proposes to update this statement as follows: **"Data:** Record the number of samples, the test speed (millimeters per minute), and the peak force value achieved kN or kilograms of force per square millimeters (kg force/mm^2). **Adjust the force reading to zero and then gradually increase the force up to the desired limit at a constant test speed (millimeters per minute).**"	Chapter states that "The procedure is based on the method described in ISO 8113…", but as currently written, the procedure is not aligned to ISO 8113, particularly in terms of the force values applied during the load test.

SECTION 4.4 Extractable Elements

Page Number	Reference Text	Proposed Change	Rationale
Pg 16	ICP-OES, ICP-AES, or ICP-MS with a perfluoroalkoxy alkane (PFA) nebulizer or spray chamber are recommended.	PDA proposes removing statement or updating the statement to include rationale for specifying use of a perfluoroalkoxy alkane (PFA) nebulizer.	Not clear why use of a perfluoroalkoxy alkane (PFA) nebulizer is recommended. PDA proposes removing statement to reduce confusion. If not feasible, would suggest providing rationale behind this recommendation for reader clarity and understanding.
Pg 16	**"Glass container preparation:** Select 6 dry containers. Remove any debris or dust. Shortly before the test,	PDA suggests updating the statement as follows:	The sample preparation method for titration is different from that for the extractables test. By making the

	fill each container to the brim with *Purified Water* and allow to stand, filled with water, for 20 ± 5 min. Empty the containers, carefully rinse (twice with water and once with *Purified Water*), and allow to drain."	**"Glass container preparation:** Select 6 containers and **carry out sample preparation using the same procedure as for the inner surface test.**"	suggested update to the statement, it will be more accurate and provide the reader with directions on which method should be used.
Pg 16	**"Fill:** Fill each glass container as per *4.2 Determination of Inner* Surface *Hydrolytic Resistance*. 90% of the brimful with *Purified Water*. Cap with polytetrafluoroethylene (PTFE) septa-lined aluminum caps or closure system utilized for the container. Report both brimful and 90% brimful volumes."	PDA recommends updating the statement as follows: **"Fill:** Fill each glass container as per *4.2 Determination of Inner* Surface *Hydrolytic Resistance*. 90% of the brimful with *Purified Water*. Cap with **appropriate** cap (**i.e., no aluminum)** or closure system utilized for the container. Report both brimful and 90% brimful volumes."	Use of a closure that contains aluminum could have a significant influence on the aluminum extraction test result. Recommend updating statement to clarify for reader that aluminum containing caps are not suitable.
Pg 16	**"Extraction conditions:** Extract according to the autoclaving procedure described under *4.2 Determination of Inner Surface Hydrolytic Resistance* at 121 ° for 1 h. 1. Prepare extraction recover samples (spikes) 20 and 120 µg/L levels, respectively. Prepare a 120 µg/L (ppb) standard solution of aluminum and arsenic in *Purified Water*. Transfer the spike solution to 4 separate analysis tubes. 2. Prepare a 20 µg/L (ppb) standard solution of	PDA proposes updating the statement as follows: **"Extraction conditions:** Extract according to the autoclaving procedure described under *4.2 Determination of Inner Surface Hydrolytic Resistance* at 121° for 1 h. 1. Prepare extraction recover samples (spikes) **50** and **150** µg/L of **As levels** and **500** and **1500** µg/L **of Al,** respectively. Prepare a **150** µg/L (ppb) standard solution of **arsenic and standard solution** of **1500 µg/L aluminum**	By updating the statement as proposed, it will align the recommendations of this Chapter with those found in *USP Chapter <211> Arsenic* and *USP Chapter <206> Aluminum*.

	aluminum and arsenic in *Purified Water*. Transfer the spike solution to 4 separate analysis tubes."	in *Purified Water*. Transfer the spike solution to 4 separate analysis tubes. 2. Prepare **50 µg/L (ppb) standard solution of arsenic and standard solution of 500 µg/L aluminum** in *Purified Water*. Transfer the spike solution to 4 separate analysis tubes.	
Pg 16	"**Analytical method**: Calibrate the instrument using reference solutions for aluminum and arsenic that span from the quantitation limit of 20-1000 µg/L (ppb)."	PDA recommends the statement as follows: **"Analytical method:** Calibrate the instrument using reference solutions that span from the quantitation limit of **50-150 µg/L (ppb) for arsenic and 50-1500 µg/L (ppb) for aluminum.**"	As currently written, the method described in USP <660> is not aligned with the method described in USP <211> and USP <206>. By making the recommended updated to the statement, it will be more accurate and will align the recommendation between the three USP Chapters.
Pg 16	**"Aluminum:** An aluminum limit is required for Type I and Type II containers. The limit does not exceed 1.0 µg/ml."	PDA proposes removing aluminum extraction limit. If not feasible, PDA recommends adding the following sentence to the statement: **"Aluminum:** An aluminum limit is required for Type I and Type II containers. The limit does not exceed 1.0 µg/ml. **Note: Test does not apply to Type III glass."**	Aluminum is of low inherent toxicity as outlined in the ICH Q3D and of concern in only specific therapy fields. The appropriateness of the proposed limit seems to be arbitrary without context to the drug product formulation and use. The ruggedness of the proposed test has high uncertainty at the proposed low levels. The limit does not take into account container size. Removal of Procedure 1 for <211> arsenic is an unnecessary and unreasonable burden to incoming laboratories that do not have capability to run Procedures 3 or 4.

			The extraction level of a Type III Glass is approximately 10 times higher compared to a Type I Glass (see also Type I and Type III limits for Na extraction), thus Type III needs to be excluded or limit has to be widened.
Pg 16	"**Arsenic:** An arsenic limit is required for Type I and Type II glass containers. The limit does not exceed 0.1mcg/ml."	PDA recommends adding statement clarifying as follows: "**Arsenic:** An arsenic limit is required for Type I and Type II glass containers. The limit does not exceed 0.1mcg/ml. **Arsenic limit is not required for Type III (i.e., soda lime silica glass containers)."**	An arsenic limit is not mentioned for Type III (i.e., soda lime silica glass containers). By adding this statement, it will highlight for the readers that this test is not applicable for Type III glass containers.

4.5 SPECTRAL TRANSMISSION FOR COLORED GLASS CONTAINERS

Table 5. Maximum Allowed Value for Specific Transmission for Colored Tubular Glass Containers

Page Number	Reference Text	Proposed Change	Rationale
Pg 17	"Table 5. Maximum Allowed Value for Specific Transmission for Colored Tubular Glass Containers"	PDA proposes updating Table 5 as provided in example below*.	Table proposal modifies tubular light transition limits to be consistent with current ISO size and legacy limits and maintains a minimum of 10% transmission for all molded containers with wall thickness over 1.4 mm.

*Table 5. Maximum Allowed Value for Specific Transmission for Colored Tubular Glass Containers

Nominal Wall Thickness (mm)		Maximum Allowed Specific Transmission Limit (% T_{max})
<=	0.29	60
0.3	0.34	55
0.35	0.39	50
0.4	0.44	45
0.45	0.49	40
0.55	0.64	35
0.65	0.74	30
0.75	0.84	25
0.85	0.94	20
0.95	1.04	15
1.05	1.39	12
>=	1.4	10

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