Containers—Glass <660>: Update

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Glass Containers: <660>

Glass Container standard has a long history in the USP

- Glass Types I , II, and III was described in USP (1940)
  - Type I (Borosilicate)
  - Type II (Treated soda-lime)
  - Type III (Soda-lime)
- The <660> *Containers Glass* (2023) is very similar to the glass chapter published in USP (1965)
- Chapter <660> is currently aligned with Pharm. Eur. Chapter 3.2.1. *Glass Containers for Pharmaceutical Use*
- Revision of <660> was initiated in 2016 with the formation of the current Expert Panel
  - The purpose of the Expert Panel is to revise <660> to delineate the tests, testing procedures, technology requirements, and specifications for the different glass quality attributes

USP Glass Chapter <660>: Expert Panel

Current Chapter

- Nomenclature: Type I Borosilicate; Type II Treated Soda-Lime-Silica; Type III Soda-Lime-Silica
- Glass Grains Test (Identity Test to distinguish Type I from Types II and III)
- Inner Surface Hydrolytic Resistance Test (distinguishes Types I and II from Type III)
- Surface Etching Test (distinguishes high hydrolytic resistance is due to either the inner surface treatment or to the chemical composition of the glass containers)
- Extractable Arsenic Test (USP <211>; Colorimetric Test)
- Spectral Transmission for Colored Glass Containers

Potential Revisions

- Nomenclature: Add treated aluminosilicate glass and quartz glass
- Glass Grains Test: Replace with a new test based on Wavelength Dispersive X-Ray Fluorescence (WDXRF)
- Inner Surface Hydrolytic Resistance Test: Retain test but provide guidance on the application of the autoclave instructions in <1660> from a new study
- Surface Etching Test: Consider replacing test (uses Hydrogen fluoride)
- Extractable Arsenic Test: Develop a new test based on ICP
- Spectral Transmission for Colored Glass Containers: Revise the test based on data from both borosilicate and soda-lime-silica colored glass

Nomenclature Options Discussed

Option 1 (Three-Tier)

Classification is based on performance and not composition. Because treated aluminosilicate and quartz meet the testing requirements for Type I glass one option could be to designate those materials, and any other, as Type I.

This concept applies the fact that "a glass of any composition that is able to pass the current Type I performance based hydrolytic resistance tests should be able to be classified as Type I glass.

Type I (Treated* or untreated)	Type II	Type III
Aluminosilicate Borosilicate Quartz	Treated Soda-lime-silica	Soda-lime-silica

* Any post manufacturing processing

Option 2 (Five-Tier)

Classification is expanded to include new tiers.

- Expand classification systems:
  - Type I: Highly resistant borosilicate glass
  - Type II: Treated soda-lime-silica glass
  - Type III: Soda-lime-silica glass
  - Type IV: Aluminosilicate glass
  - Type V: Quartz glass
    - Maintains global harmonization of the Type I, Type II and Type III definition

Type I	Type II	Type III	Type IV	Type V
Borosilicate	Treated Soda-lime-silica	Soda-lime-silica	Aluminosilicate	Quartz

Nomenclature Options: Drawbacks

- Market Research mentioned that borosilicate, aluminosilicate and quartz are different materials and Option 1 does not differentiate. Also, there was the perception that this option was less precise / ambiguous.

Type I (Treated or Untreated)	Type II	Type III
Aluminosilicate Borosilicate Quartz	Treated Soda-lime silica	Soda-lime silica

Option 1

- Market Research mentioned that using sub-tiers for Type 1 would maintain focus on performance and add specificity

- Option 1B was discussed by the Expert Panel, and it was agreed to not divide Type I into sub-tier in order to avoid the creation of a perception of quality tiering (composition and identity)

	Type I
Class A	Borosilicate
Class B	Aluminosilicate
Class C	Quartz

Option 1B

- Market Research showed that Option 2 created the perception of quality tiering (Laddering).

Type I	Type II	Type III	Type IV	Type V
Borosilicate	Treated Soda-lime silica	Soda-lime silica	Aluminosilicate	Quartz

FDA Letter

FDA U.S. FOOD & DRUG ADMINISTRATION

November 01, 2022

Ms. Jessica Simpson
Senior Manager, Executive Secretariat
The United States Pharmacopeial Convention, Inc.
12601 Twinbrook Parkway
Rockville, MD 20852

REF: 11-22-002-AB

Dear Ms. Simpson:

This letter reiterates FDA's recommendations on pharmaceutical glass type classification. In 2017, FDA provided USP a recommendation to revise the definition of Type I glass from composition-based characteristics to performance-based characteristics to allow for innovation in the manufacturing of glass intended for parenteral packaging. We shared published information to support this recommendation and noted that a performance-based classification instead of a chemical composition-based classification would be beneficial for public health.[1] Over the last two years, there have been reported global shortages of glass vials, potentially creating a bottleneck for the delivery of the COVID-19 vaccine and threatening the availability of some existing parenteral products.

FDA is supportive of the use of new glass compositions if they demonstrate equivalent or superior performance characteristics such as improved thermal and hydrolytic resistance compared to the current compendial glass compositions and demonstrate suitability for the drug product; however, restrictive compendial definitions have impeded adoption of new glass compositions with such characteristics. Several official monographs specify the use of specific glass chemical composition; drug product manufacturers submitting a drug application to FDA in which they have proposed use of glass that performs equivalently (based on testing) but differs in chemical composition will face additional time-consuming administrative steps during consideration for FDA approval (See Federal Food, Drug, and Cosmetic Act, Section 502(g)).

FDA appreciates the engagement and dialogue with USP staff and expert volunteers to determine the best path forward with no adverse impact on current marketed products. To retain the strict scientific standards for glass packaging while maintaining inclusivity for new glass compositions, FDA strongly recommends that glass be defined by its performance characteristics and not solely on its composition. We are supportive of an approach to rapidly revise the definition of Type I glass (as found in the latest proposal of General Chapter <660> *Containers – Glass*) while concurrently updating monograph requirements with language reflecting the new performance-based Type I glass definition.

[1] Schaut, R. A., Peanasky, J. S., DeMartino, S. E., & Schiefelbein, S. L. (2014). A new glass option for parenteral packaging. PDA journal of pharmaceutical science and technology, 68(5), 527–534. https://doi.org/10.5731/pdajpst.2014.00998

1. Request revision of USP Type 1 definition from composition-based to performance based
2. Global issues regarding glass production and concerned about resulting drug shortages
3. Supportive of the use of new glass compositions that are not currently outlined in the USP, if they demonstrate equivalency or superior performance to Type 1 Borosilicate Glass, along with demonstrating suitability for the product
    a) Restrictive compendial definitions is impeding the adoption of new glass compositions with desirable characteristics.
4. Several drug product monographs specify the use of specific glass composition which is delaying drug approvals
5. FDA Request
    a) Revise <660>
    b) Revise applicable monographs
    c) Revise as quickly as possible

Possible Solution for Increasing Chapter Flexibility

<660> Revision

1. Remove glass classification base on composition
    a) Type I (Borosilicate Glass)
    b) Type II (Treated Soda-lime Silica)
    c) Type III (Soda-lime Silica)
2. Define Type I, II, and III containers by its performance
3. No change to test procedures or acceptance criteria

Proposed: <660> Revision

(660) CONTAINERS—GLASS

DESCRIPTION

~~Glass containers for pharmaceutical use are intended to come into direct contact with pharmaceutical products.~~ ~~Glass used for pharmaceutical containers is either borosilicate (neutral) glass or soda-lime-silica glass. Borosilicate glass contains significant amounts of boric oxide, aluminum oxide, and alkali and/or alkaline earth oxides in the glass network. Borosilicate glass has a high hydrolytic resistance and a high thermal shock resistance due to the chemical composition of the glass itself; it is classified as Type I glass. Soda-lime-silica glass is a silica glass containing alkaline metal oxides, mainly sodium oxide, and alkaline earth oxides, mainly calcium oxide, in the glass network. Soda-lime-silica glass has a moderate hydrolytic resistance due to the chemical composition of the glass itself; it is classified as Type III glass. Suitable treatment of the inner surface of Type III soda-lime-silica glass containers will raise the hydrolytic resistance from a moderate to a high level, changing the classification of the glass to Type II.~~

Glass containers for pharmaceutical use are intended to come into direct contact with pharmaceutical products. The following recommendations can be made as to the suitability of ~~the~~ a glass ~~type for~~ containers for pharmaceutical products, based on the tests for hydrolytic resistance. ~~Type I g~~Glass containers meeting Type I performance are suitable for most products for parenteral and nonparenteral uses (e.g. borosilicate). ~~Type II g~~Glass containers meeting Type II performance are suitable for most acidic and neutral aqueous products for parenteral and nonparenteral uses (e.g. treated soda-lime silica). ~~Type II g~~Glass containers meeting Type II performance may be used for alkaline parenteral products where stability data demonstrate their suitability. ~~Type III G~~glass containers meeting Type III performance (e.g. soda-lime silica) usually are not used for parenteral products or for powders for parenteral use, except where suitable stability test data indicate that ~~Type~~ containers meeting Type III performance ~~III glass~~ is satisfactory.

SPECIFIC TESTS

The *Glass Grains Test* combined with the *Surface Glass Test* for hydrolytic resistance determines ~~the~~ glass ~~type~~performance. The hydrolytic resistance is determined by the quantity of alkali released from the glass under the conditions specified. This quantity of alkali is extremely small in the case of the more resistant glasses, thus calling for particular attention to all details of the tests and the use of apparatus of high quality and precision. Conducting these tests in conjunction with a glass standard reference material (SRM) on a routine basis will help to ensure the accuracy of the method. 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. The tests should be conducted in an area relatively free from fumes and excessive dust. Test selection is shown in *Table 1* and *Table 2*.

Table 1. Determination of Glass ~~Types~~Performance

~~Container~~ Type	Test	Reason
I, II, III	*Glass Grains Test*	Distinguishes Type I ~~borosilicate glass~~ from Type II and III ~~soda-lime-silica glass~~

The inner surface of glass containers is the contact surface for pharmaceutical preparations, and the quality of this surface is determined by the *Surface Glass Test* for hydrolytic resistance. The *Surface Etching Test* may be used to determine whether high hydrolytic resistance is due to chemical composition or to surface treatement. Alternatively, the comparison of data from the *Glass Grains Test* and the *Surface Glass Test* may be used in *Table 2*.

Table 2. Determination of Inner Surface Hydrolytic Resistance

~~Container~~ Type	Test	Reason
I, II, III	*Surface Glass Test*	Determines hydrolytic resistance of inner surface; distinguishes between *Type I* and *Type II* containers with high hydrolytic resistance and *Type III* containers with moderate hydrolytic resistance
I, II	*Surface Etching Test* or comparison of *Glass Grains Test* and *Surface Glass Test* data	Where it is necessary, determines whether high hydrolytic resistance is due to inner surface treatment or to the chemical composition of the glass containers

Accelerated Revision (Proposed IRA): <660>

Timeline

- **Revision Draft Finalized:** Jan 2023
  - <660>: Focused Revision
    - Revise to focus on “Type I Performance” vs. “Type I Glass Material”
- **Publication Submission:** Feb 2023
- **PF Posting:** March 2023
- **Commenting Deadline:** May 2023*
- **Ballot Vote:** June 2023
- **IRA Posting Date:** July 2023
- **IRA Official Date:** Sept. 2023

Chapter <660>

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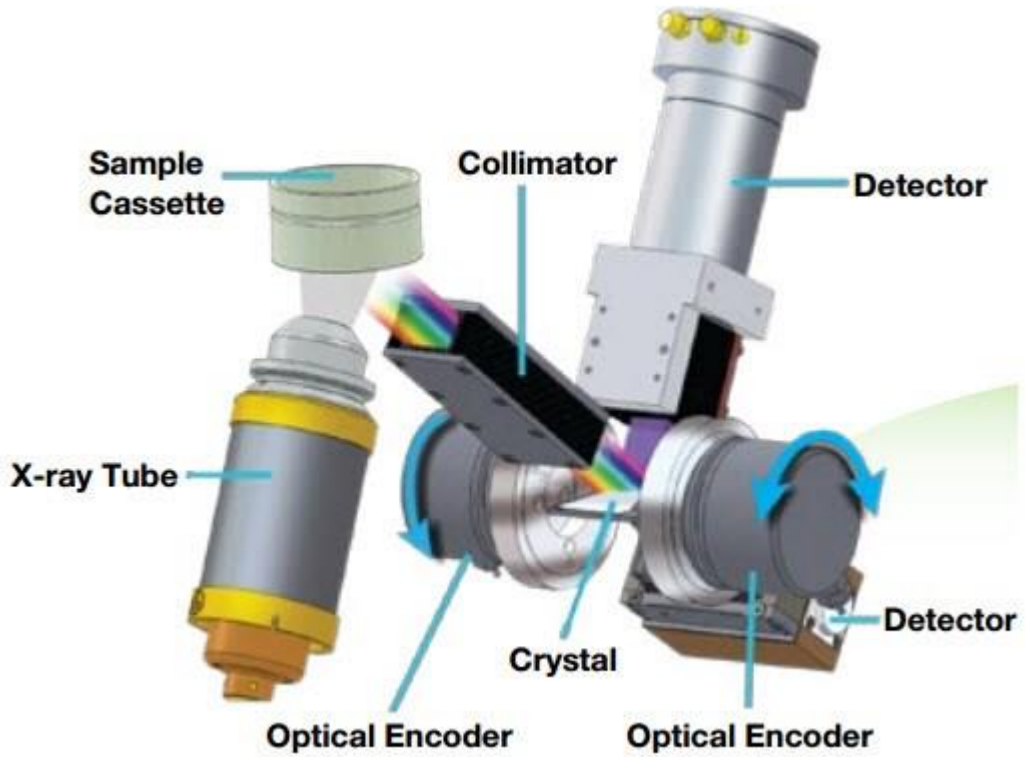
USP Glass Chapter <660>: Potential Revision

Glass Grains Test:

- Current test will not distinguish aluminosilicate, quartz, or borosilicate glass
  - New test is needed to distinguish between the 4 glass “families”
    - Aluminosilicate
    - Borosilicate
    - Quartz
    - Soda-lime-silica
- Elemental Composition by Wavelength Dispersive X-Ray Fluorescence (WDXRF) potential test



WDXRF Study Design

- WDXRF Spectrometer
  - An X-ray fluorescence spectrometer with a minimum 3kW power and ≤ 32 or ≥ 27 mm mask capable of measuring boron
- Laboratory Oven
  - Capable of achieving >1000°C
    - Quartz requires 1800°C
  - Produces a round glass puck polished one side with a mirror finish
- Glass Samples
  - Tubular
    - Aluminosilicate, Borosilicate (33,51,70 expansion), Quartz, Soda-Lime-Silica
  - Molded
    - Borosilicate (80 exp), Soda-Lime-Silica
  - Clear
    - Aluminosilicate, Borosilicate (33,51,70), Quartz, Soda-Lime-Silica
  - Amber:
    - Borosilicate (51,70 exp), Soda-Lime-Silica

Chemical Composition Range of Glass Families

Wavelength Dispersive X-Ray Fluorescence (WDXRF)

Chemical Composition Wt %	Quartz Glass	Alumino-silicate Glass	Borosilicate Glass Ca. 33 Expansion	Borosilicate Glass Ca. 51 Expansion	Borosilicate Glass Ca. 70 Expansion	Soda-Lime-Silica Glass
Silicon Dioxide (SiO_2)	> 99	70 - 80	78 - 82	70 - 76	65 - 73	69 - 75
Aluminum Oxide (Al_2O_3)		6 - 12	2 - 3.5	4.5 - 7	4.5 - 7	0.5 - 4
Boric Oxide (B_2O_3)		< 1	10 - 13	8 - 12	5 - 8	0 - 1
Sum Alkali Metal Oxides (Na_2O and K_2O)		8 - 13	3 - 5	6 - 8	10 - 12	12 – 16
Sum Alkaline Earth Metal Oxides (CaO, MgO, BaO)		3 - 7	< 0.2	1 - 3	4 - 9	10 – 15

Identification by Chemical Composition

- The data obtained indicated that analysis of glass containers samples using WDXRF provides accurate compositional data
- This data provides a scientific basis for a Decision Tree that can identify the 4 glass families by chemical composition – Aluminosilicate, Borosilicate, Quartz, Soda-Lime-Silica
- In addition, it allows an approach to identify the sub-groups of Borosilicate glass based on the Coefficient of Expansion (ca. 31, 51, 70)

USP Glass Chapter <660>: Potential Revision

Spectral Transmission for Colored Glass Containers

- Light transmission method was added to the USP in 1940, with the basis of the current method appearing in USP in 1955.
- The current spectral transmission requirement measures light transmission in the range of 290–450 nm continuously or at intervals of 20 nm
  - Method is in alignment with the European Pharmacopoeia
- Requirements in <660> differentiate between glass containers for parenteral and non-parenteral drug products.
  - Acceptance criteria for parenteral drug products are shown in table
  - Acceptance criteria for non-parenteral drug products is a single maximum value of 10% at all wall thickness and any wavelength in the range of 290–450 nm.

Limits of Spectral Transmission for Colored Glass Containers for Parenteral Products

Nominal Volume (mL)	Maximum Percentage of Spectral Transmission at Any Wavelength between 290 and 450 nm	
	Flame-Sealed Containers	Containers with Closures
NMT 1	50	25
1–2	45	20
2–5	40	15
5–10	35	13
10–20	30	12
NLT 20	25	10

USP Glass Chapter <660>: Potential Revision

- The amount of light that passes through the glass wall depends on the glass composition
  - Annealing time and temperature, and the wall thickness.
- Concerning the composition for colored glass containers;
  - Type I borosilicate glass, typically iron and titanium are used to color the glass
  - Type II and III soda-lime-silica glass, typically iron and manganese are used to color the glass
- Current glass container market is not standardized, thus there is no reliable correlation between filling volume and the wall thickness.
- **Current thesis:** More scientifically sound to correlate spectral transmission to the wall thickness of the glass containers rather than filling volume.

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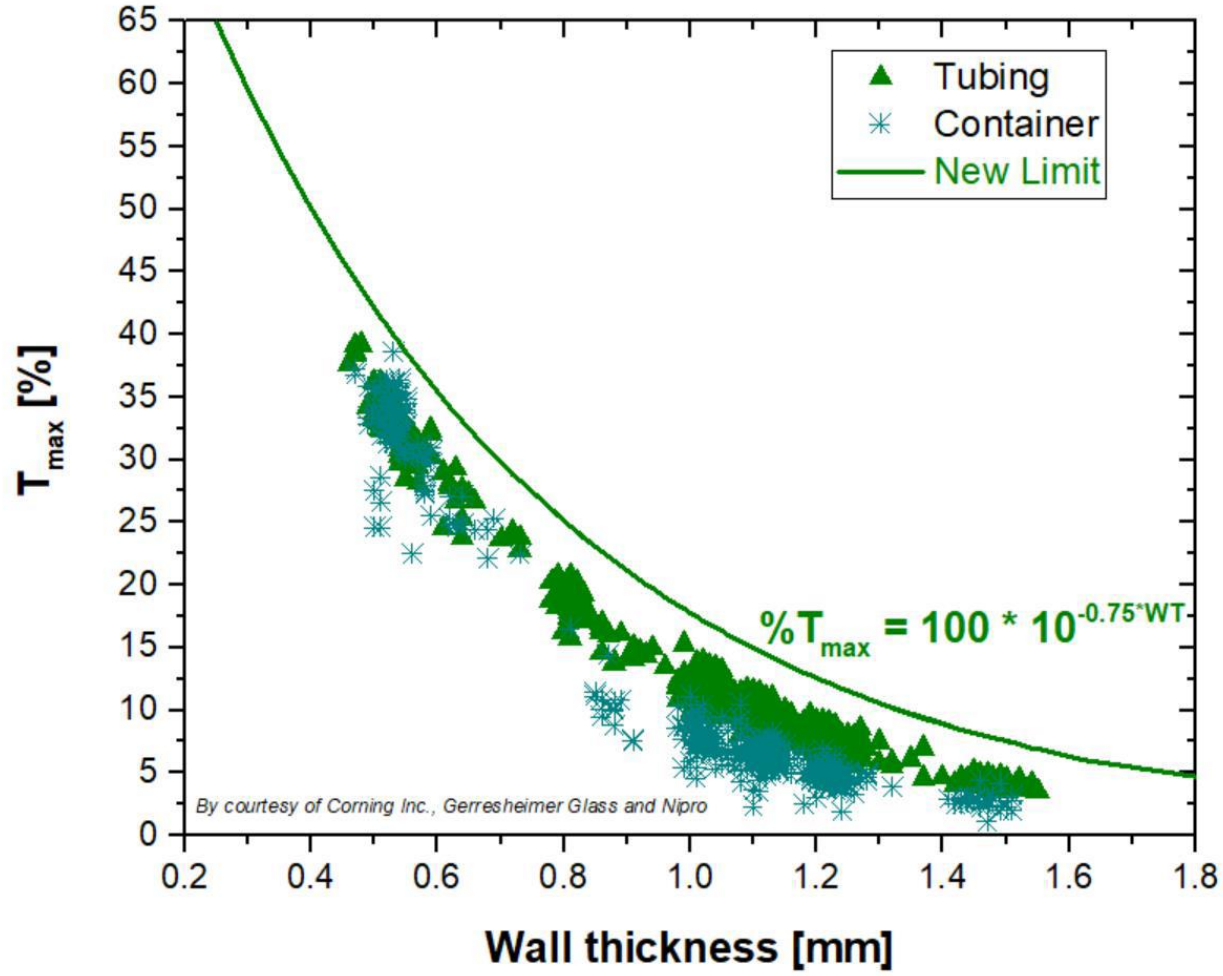
10–20	30	12
NLT 20	25	10

USP Glass Chapter <660>: Potential Revision

- A research protocol was designed to assess our current thesis and the validity of the current specifications for colored containers.
- The selected parameters were:
  - Glass containers: Ampules, bottles, vials, cartridges, and syringes
  - Manufacturing process: Tubular and molded
  - Glass: Borosilicate and soda-lime-silica glass
  - Tubular glass coefficient of thermal expansion (CTE)
    - Borosilicate (ca. 3.0–5.0 × 10−7/K − 6.0 × 10−7/K)
    - Low boron borosilicate (ca. 8.0 × 10−7/K)
    - Soda-lime-silica (ca. 8.0–9.0 × 10−7/K)
  - Molded glass CTE:
    - Borosilicate (ca. 6.0 × 10−7/K)
    - Soda-lime-silica (ca. 8.0–9.0 × 10−7/K)
  - Container WT: mm
  - Data: Plot wall thickness versus light transmission

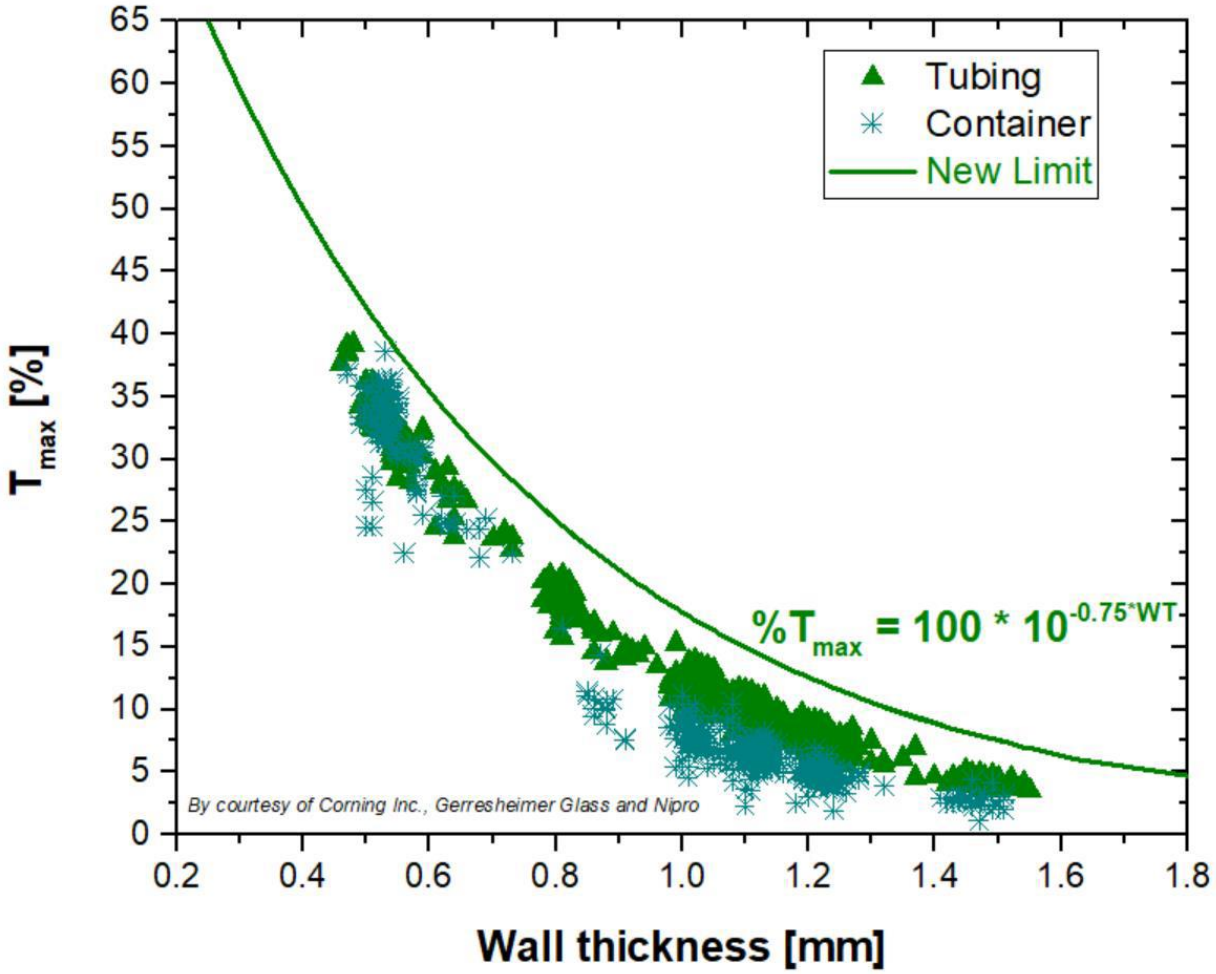
Spectral Transmission for Type I Tubular Colored Glass Containers



USP Glass Chapter <660>: Potential Revision

- Wall thickness of tubular containers is relatively constant
  - Glass manufacturers can supply data on wall thickness for their containers type;
  - Or the thickness can be measured by the end user
- USP collected data that covered three years of glass tubing and glass container production
- Data analyzed for light transmission showed that a mathematical equation could be established between wall thickness and light transmittance
  - %Tmax could be calculated for every WT, including a safety margin using the following equation: $\%T_{max} = 100 * 10^{-0.75*WT}$

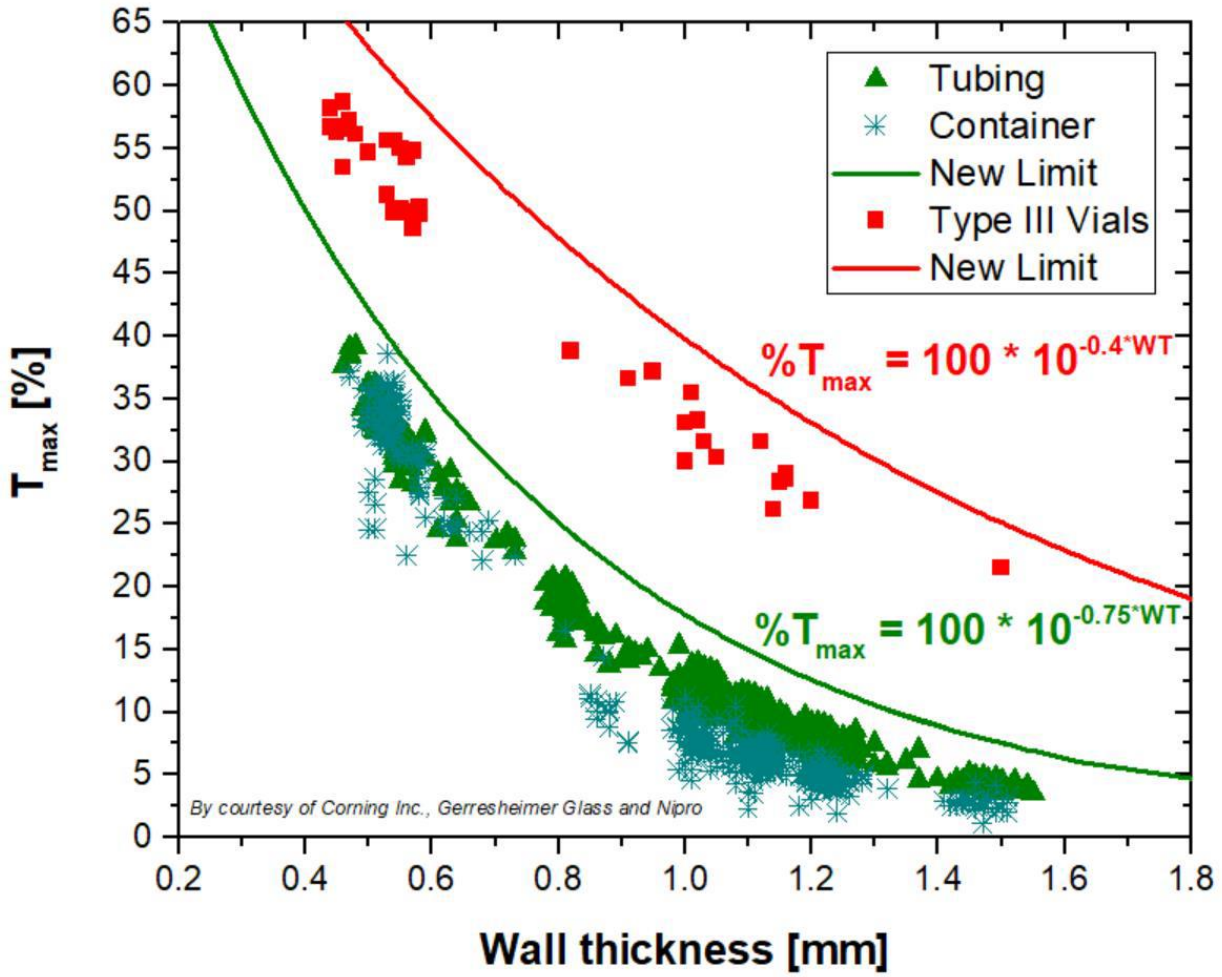
Spectral Transmission for Type I Tubular Colored Glass Containers



USP Glass Chapter <660>: Potential Revision

- The obtained data indicated that Type II and III tubular glass containers does not fit the equation established for tubular Type I containers,
- Second equation for Type II and II containers would be required
  - %Tmax could be calculated for every WT, including a safety margin using the following equation: $\%T_{max} = 100 * 10^{-0.40*WT}$
- Molded containers because they are produced by either blow-and-blow or press-and-blow processes wall thicknesses of the side wall and base can
  - Using wall thickness is not appropriate for molded containers
  - Thus, a single value minimum allowed transmittance value is proposed for all molded amber glass containers.

Spectral Transmission for Type III Colored Glass Containers



USP Glass Chapter <660>: Potential Revision

Spectral Transmission for Colored Glass Containers

- Use the following calculations for Maximum Allowed Spectral Transmission
  - WT = Wall Thickness (mm)
    - Type I Containers:
      - $\%T_{max} = 100 * 10^{-0.75*WT}$
    - Type II and III Containers:
      - $\%T_{max} = 100 * 10^{-0.4*WT}$
- Molded Containers (I, II, and III) have a maximum allowed transmission of 10%, regardless of the wall thickness

Maximum Allowed Value for Specific Transmission for Colored Tubular Glass Containers

Nominal Wall Thickness (mm)	Maximum Allowed Specific Transmission ($\%T_{max}$)	
	Borosilicate Tubular Containers	Soda-Lime-Silica Tubular Containers
≤0.51	50	66
≥0.51–0.6	42	63
≥0.61–0.7	35	58
≥0.71–0.8	30	52
≥0.81–0.9	25	48
≥0.91–1.0	21	44
≥1.01–1.1	18	40
≥1.11–1.2	15	36
≥1.21–1.3	13	33
≥1.31–1.4	11	30
≥1.41–1.5	9	28
≥1.51–1.6	7	25
≥1.61–1.7	6	23
≥1.71–1.8	5	21
≥1.81–1.9	4	19
≥1.91	4	17

USP Glass Chapter <660>: Potential Revision

Proposed changes to <660> *Containers – Glass*

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- Glass Grains Test: Replace with a new test based on Wavelength Dispersive X-Ray Fluorescence (WDXRF)
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Glass Chapters Revision Proposal

<660> Containers-Glass

<1660> Evaluation of the Inner Surface Durability of Glass Containers

- **Published:** PF 50 (5) September 2024
- **Comment Deadline:** November 31, 2024

Thank You

The standard of trust