Update on USP's General Chapters on Biological Reactivity, Extractables and Leachables, and Glass Containers

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Michael Eakins, Ph.D.

Principal Consultant, Eakins & Associates

Vice-Chair USP General Chapters Packaging and Distribution Expert Committee

Agenda

Revision of USP Bioreactivity, Extractables & Leachables, and Glass Containers Chapters

- Bioreactivity chapters
  - <87>, <88>, <1031>, <1184>
- Extractables & Leachables chapters
  - <1663>, <1664>
- Glass Containers chapters
  - <660>, <1660>

Biological Reactivity Tests <87>, <88>, <1031>, <1184>

- <87> *Biological Reactivity Tests, In Vitro* official in USP XXII (1990)
- <88> *Biological Reactivity Tests, In Vivo* official in USP XXII (1990)
- <1031> *The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants* <1031> official in USP 25 – NF 20 (2002)
  - <1031> was written to provide guidance on the identification and performance of procedures for evaluating the biocompatibility of drug containers, elastomeric closures, medical devices, and implants
- <1184> *Sensitization Testing* official in USP 30 – NF 25 S1 (2007)

Revision of USP Bioreactivity Chapters

- In 2015 the USP Toxicology Expert Committee was disbanded
  - Chapters <87>, <88>, <1031>, and <1184> were transferred to the USP Packaging and Distribution Expert Committee (PD EC)
  - A PD EC Expert Panel was formed to revise these chapters
- Objectives of the Expert Panel:
  - Reduce the amount of redundant bioreactivity testing of existing plastic and elastomeric materials
  - Eliminate unnecessary animal testing for new materials
  - Refine the type of testing performed to align with the potential risk
  - Replace outdated tests with new tests
  - Align specifications with relevant ISO 10993 standards where possible
- USP Stimuli Article "*USP's Approach for Future Revision of Biological Reactivity Chapters* <87>, <88>, and <1031>" published in PF 46(4), 2020
- Revisions of <87>, <88>, and <1031> published in PF 47(4), 2021

Revision of Biological Reactivity Tests, In Vitro ⟨87⟩

- **Revise Cytotoxicity Tests**
  - Agar Diffusion Test deleted
  - Neutral Red Uptake (NRU) Test added
  - Align tests with ISO 10993-5 (2009) *Tests for In Vitro Cytotoxicity*
- **Genotoxicity Tests**
  - Four genotoxicity tests added
  - Align tests with ISO 10993-3 (2014) *Tests for Genotoxicity*

Revision of Biological Reactivity Tests, In Vivo ⟨88⟩

- **Classification of Plastics deleted since the distinction of plastic materials into six classes (Class I to Class VI) no longer serves a purpose – in practice only Class VI is utilized by vendors and end-users**
- **Class VI Classification replaced by the term "*Pharmaceutical Grade Polymeric Materials*" utilizing the same test procedures as for Class VI for plastic and elastomeric materials for packaging/delivery systems**
- **Move Sensitization Tests from <1184> into <88> and delete <1184>**

The Biocompatibility of Materials Used in Drug Containers, Medical Devices, and Implants <1031>

- Title changed to *The Biocompatibility of Pharmaceutical Packaging/Delivery Systems and their Materials of Construction* <1031>
- Chapter scope encompasses plastic materials of construction and plastic and elastomeric components for pharmaceutical packaging/delivery systems and packaging of combination products
- Designed to support and explain revised <87> and <88>

The Biocompatibility of Pharmaceutical Packaging/Delivery Systems and their Materials of Construction <1031>

- No longer covers medical devices and implants, but does cover combination products
- Regulation of a combination product is assigned to either FDA Center for Biologics Evaluation and Research (CBER), Center for Drug Evaluation and Research (CDER), or Center for Devices and Radiological Health (CDRH) based on a determination of which constituent part provides the primary mode of action (PMOA) for the combination product
- This distinction is important since the expectation of CDRH for which bioreactivity tests are performed can differ from the expectations of CDER and CBER

The Biocompatibility of Pharmaceutical Packaging/Delivery Systems and their Materials of Construction <1031>

Changes: addition of sections covering:

- Overview of Biocompatibility Evaluation
  - Pharmaceutical Grade Polymeric Materials
  - Regulatory Expectations
- Risk-based Approach to Biocompatibility Evaluation
- Biological Reactivity Test Considerations
- Investigating a Biological Reactivity Test Failure
- Chemical Assessment
- Overall Biocompatibility Evaluation
- Glossary
- References

The Biocompatibility of Pharmaceutical Packaging/Delivery Systems and their Materials of Construction <1031>

Chemical Assessment

- Assessment of biocompatibility or biological reactivity may be both complemented and supplemented by chemical characterization and individual chemical safety assessment (CSA) of extractables from the packaging/delivery system
- A CSA can play a complementary role:
  - Provides an understanding of packaging components and their materials of construction, as well as the chemical entities that can potentially leach from them
  - Assists with biocompatibility test failure analysis by potentially providing a clear and scientifically sound rationale for such failures
  - Plays an important role in supporting the elimination of unnecessary in vivo testing
  - Informs appropriate biocompatibility endpoint evaluation

The Biocompatibility of Pharmaceutical Packaging/Delivery Systems and their Materials of Construction <1031>

- Chemical Assessment (Considerations):
  - Information and Prior Knowledge
  - Generating the Extract
  - Characterizing the Extract
- Chemical Safety Assessment of E&L
- Chemical Safety Assessment Methodology: PDE Derivation
  - Provides Example
- 3 Case Studies

The Biocompatibility of Pharmaceutical Packaging/Delivery Systems and their Materials of Construction <1031>

Overall Biocompatibility Evaluation

The biocompatibility evaluation should take into consideration:

- The intended use
- The patient population
- The duration of use
- The review of all data such as:
  - Biological reactivity testing
  - Chemical characterization with associated safety assessment
  - Physicochemical testing
  - Literature and previous clinical experience

Publication of Revised Chapters in Pharmacopeial Forum

- Revised Chapters <87>, <88>, and <1031> were published in the Pharmacopeial Forum (PF) 47(4) July – August, 2021
- Comment Period was 3 months
- Comments Received

USP Chapter	<87>	<88>	<1031>
Number of Commentators	12	14	16
Number of Comments	40	50	103

- Comments have been reviewed by the PD EC Bioreactivity Sub Committee
- Revised Chapters will be published in the PF in 4Q/2022

Extractables & Leachables: History of Product Quality Research Institute (PQRI) Best Practices

- "Safety Thresholds and Best Practices for Extractables and Leachables in OINDP" was published in 2006
- The Parenteral and Ophthalmic Drug Product (PODP) E&L Working Group was formed in 2008
- The proposed PODP identification and qualification thresholds were published as a manuscript in 2013 and subsequently revised and republished in 12/2021 as "Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products (Intravenous, Subcutaneous, and Intramuscular)"
  - [NOTE. Intrathecal, intra-cerebroventricular, intra-articular, epidural, and perineural routes are out of scope]
- Extractables and leachables assessments of ophthalmic products were published in a separate manuscript entitled, "Principles for Management of Extractables and Leachables in Ophthalmic Drug Products" due to their unique considerations in 12/2021

Publication of Two New Extractables & Leachables Product Quality Research Institute (PQRI) Documents

1. Safety Thresholds and Best Demonstrated Practices for Extractables and Leachables in Parenteral Drug Products (Intravenous, Subcutaneous, and Intramuscular)

- Submitted to the PQRI Development Technical Committee, PQRI Steering Committee and US Food and Drug Administration by the PQRI PODP Leachables and Extractables Working Group
- 28 October 2021
- 94 Pages
- Available as a Free Download from PDA (https://www.pda.org/bookstore/pda-bookstore)

Publication of Two New Extractables & Leachables Product Quality Research Institute (PQRI) Best Practices

2. Principles for Management of Extractables and Leachables in Ophthalmic Drug Products. C. T. Houston et al. *PDA Journal of Pharmaceutical Science and Technology* (2022), 28 October 2021

- 47 Pages
- PDA Journal of Pharmaceutical Science and Technology February 2022 pdajpst.2022.012744; DOI: https://doi.org/10.5731/pdajpst.2022.012744

USP Chapters on Extractables <1663> and Leachables <1664>

Three Extractables & Leachables General Information Chapters were published in USP 38 (2015)

- **<1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems**
- **<1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems**
- **<1664.1> Orally Inhaled and Nasal Drug Products**
  - **Based on PQRI's "Safety Thresholds and Best Practices for Extractables and Leachables in OINDP"**
  - **Reduced from 263 pages in PQRI to 7 pages in <1664.1>**

Extractables & Leachables: ICH Q3E

- ICH Q3E Concept Paper. “Impurity: Assessment and Control of Extractables and Leachables for Pharmaceuticals and Biologics” 6/2019
- Key Proposed Milestones for ICH Q3E
  - Step 1. Sign-off, 11/2022
  - Step 2a/b. Endorsement
  - Step 3. Public Consultation Period, 1/2023 – 6/2023
  - Step 4. Adoption 11/2024
- Perceived Problem
  - No harmonized guidance and international agreement on E&L management and control strategies exists addressing multiple dosage forms, e.g. reporting, identification and qualification thresholds and alignment on risk-based-approach and quality-by-design

Extractables and Leachables: ICH Q3E

- ICH Q3E Concept Paper. “Impurity: Assessment and Control of Extractables and Leachables for Pharmaceuticals and Biologics” 6/2019
- Expected Benefits:
  - Alignment of E&L guidance framework
  - Allow E&L control strategies to be aligned with other critical quality attributes applied to container-closure system, combination product device parts, and single-use manufacturing systems
  - Development of a single set of thresholds for reporting, identifying, and qualifying leachables covering all drug product dosage forms
  - Establish limits that are relevant to route of administration, drug indication, and patient exposure
  - Establish a global guidance framework and align pharmacopoeias. This would negate the need to revise / establish further regional pharmacopoeial guidance

Extractables & Leachables: Pharm. Eur.

Proposed New Chapter in Pharm. Eur.

- 2.4.35. *Extractable Elements in Plastic Materials for Pharmaceutical Use*
- Pharmeuropa Supporting Technical Information, May 2020
- EDQM conference to launch 11th Edition Pharm. Eur. (19 — 21, September 2022; Strasbourg)
  - Round table topic (Sept. 20) "Elemental Impurities in Plastic Materials"

Revision of USP Extractables & Leachables Chapters

Revision of USP <1663> and <1664>

- Beginning 2Q — 3Q 2023
- Revision of <1663> to take account of ICH Q3E and for updated scientific thinking
- Revision of <1664> to take account of ICH Q3E incorporation of the new PQRI recommendations, e.g.
  - <1664.2> Parenteral Drug Products
  - <1664.3> Ophthalmic Drug Products

Revision of USP Glass Chapters <660> and <1660>

Glass Containers chapters have a long history in the USP

- Glass Types I, II, and III are described in USP 12 (1940) and the current chapter <660> *Containers – Glass* in USP 45 (2022) is very similar to the glass chapter published in USP 17 (1965)
- Chapter <660> is currently aligned with Pharm. Eur. Chapter 3.2.1. *Glass Containers for Pharmaceutical Use*
- <1660> *Evaluation of the Inner Surface Durability of Glass Containers* was published in USP 37 (2014)
- Revision of <660> and <1660> was initiated in 2015 using a PDEC Expert Panel

Revision of USP Glass Chapter <660>

The current <660> *Containers – Glass* chapter contains the following descriptions/tests:

- **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**

Revision of USP Glass Chapter <660>

Proposed changes to <660> *Containers – Glass*

- 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
- 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

Revision of USP Glass Chapter <660>

- **Glass Grains Test: Replace with WDXRF**
  - **Current test will not distinguish aluminosilicate glass from borosilicate glass**
  - **Replace with a new test based on Wavelength Dispersive X-Ray Fluorescence (WDXRF)**
  - **WDXRF test has been developed by 3 external labs**
  - **Test method should distinguish between the 4 glass “families” (Aluminosilicate, Borosilicate, Quartz, Soda-lime-silica)**

WDXRF Study Design

- **WDXRF Spectrometer**
  - ≥ 3 kW; ≤ 32 mm or ≥ 27 mm mask diameter
  - Capability to measure Boron
  - ASTM E1621-13 *Standard Guide for Elemental Analysis by Wavelength Dispersive X-Ray Fluorescence Spectrometry*
- **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, BS (33,51,70), Quartz, SLS
  - Amber: BS (51,70 exp), SLS

Chemical Composition Range of Glass Families

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

WDXRF Boron Measurement

Boron's low atomic number and low K-shell energy cause various issues for XRF analysis. Because the energy of boron Kα radiation is so low (183 ev), only a thin 0.6 µm (600 nm) surface layer of the sample can be analyzed.

The following steps improved the assay reliability:

- **Optimize the emission of boron photons from the sample by using the highest available tube current at the lowest possible voltage**
- **Prepare the glass samples to be analyzed with a good surface finish – a polished glass Puck**
- **Ensure interference correction of both the background and peak position to obtain a good net intensity for boron by utilizing a sufficient number of glass standards**

WDXRF Boron Measurement

- A collaborative study into the determination of boron in glass using x-ray fluorescence (XRF) spectroscopy: An International Commission on Glass Technical Committee 2 – Chemical Durability and Analysis report.
- Guadagnino E., Sunberg, P, Brochot D. Glass Technology – European J Glass Science Technology Part A. Volume 47, Number 4, August 2006, 103-111.
- Guadagnino, E., Sundberg, P., Michiels, D., Brochot, D. A collaborative study into the determination of boron in glass using X-ray fluorescence (XRF) spectroscopy. ICG/TC2 report, 2006.
- Boron in Glass Determination Using WDXRF. A. Seyfarth
  - Journal International Centre for Diffraction Data 2008, 269-274.

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 to be constructed that identifies the 4 glass families by chemical composition – Aluminosilicate, Borosilicate, Quartz, Soda-Lime-Silica to replace the Glass Grains Test
- In addition it allows an approach to identify the sub-groups of Borosilicate glass based on the Coefficient of Expansion (ca. 31, 51, 70)

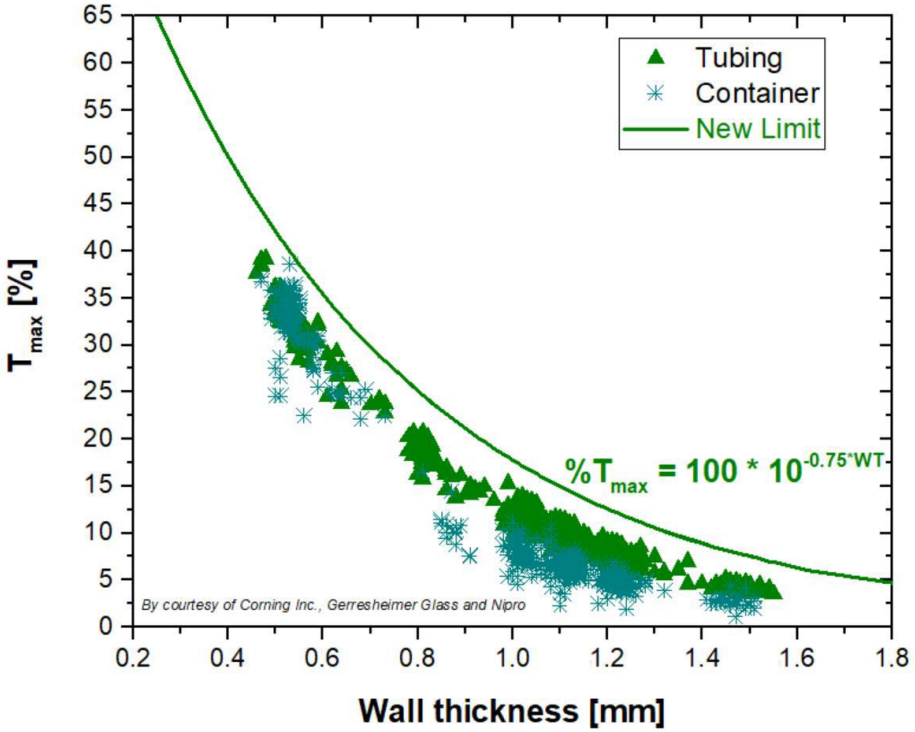
Revision of USP Glass Chapter <660>

Spectral Transmission for Colored Glass Containers

- The current spectral transmission requirements differentiate between ampules and containers with closures. A parenteral drug product packaged in both ampules and vials will have different specifications for light protection
- There is also a difference between parenteral and non-parenteral drug products; acceptance criteria for non-parenteral drug products is a single value of maximum 10% at all wall thickness and any wavelength in the range of 290–450 nm while parenteral products limits are stepwise according to filling volume
- Replace with a new test based upon wall thickness rather than container volume
- Data collected from glass vendors and analyzed

Revision of USP Glass Chapter <660>

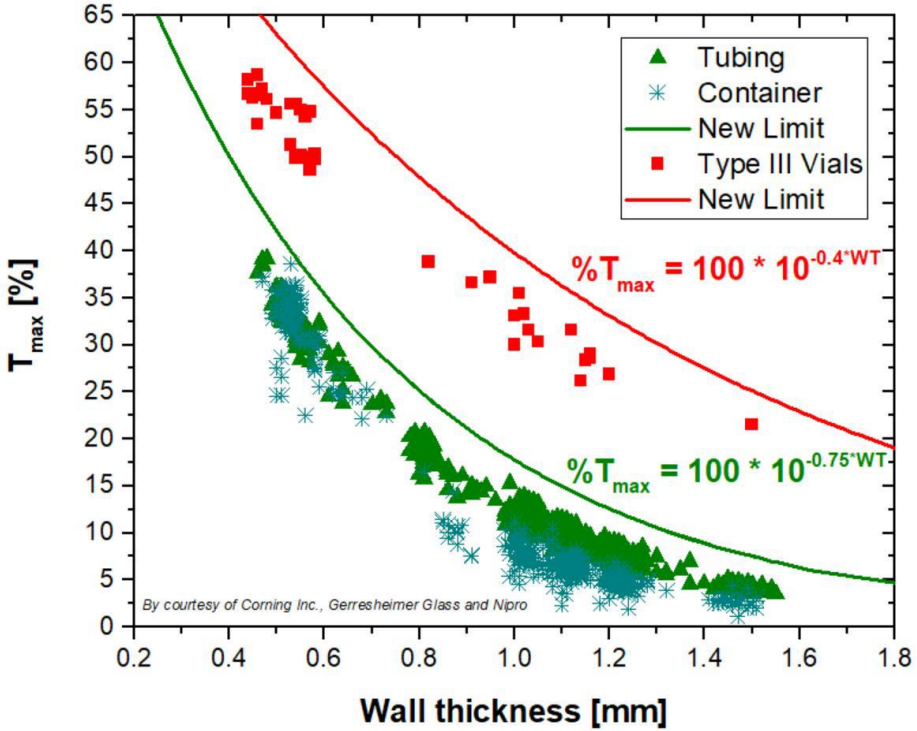
- Spectral Transmission for Type I Tubular Colored Glass Containers



USP Stimuli Article.
The Measurement of the Protective Properties of Amber Glass Containers
Boltres, B. et al.
USP Pharmacopeial Forum 47(4) 2021

Revision of USP Glass Chapter <660>

- Spectral Transmission for Type III Colored Glass Containers



USP Stimuli Article.
The Measurement of the Protective Properties of Amber Glass Containers
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Revision of USP Glass Chapter <660>

- **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 have a maximum allowed transmission of 10%, regardless of the wall thickness**

Thank You

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