U.S. PHARMACOPEIA
The Standard of Quality℠

Extractables and Leachables: Past, Present and Future

Anthony J. DeStefano, Ph.D.
Vice President, General Chapters
US Pharmacopeia

Agenda

- Past
  - USP: First Container Standards
  - Biological & Physiochemical Standards
  - <87> Biological Reactivity, In Vitro
  - <88> Biological Reactivity, In Vivo
  - <381> Elastomeric Closures for Injections
- Present
  - General Chapter Overview
  - General Chapter —Current Status
  - Importance
- Future
  - <87>/<88> Biological Reactivity, In Vitro/In Vivo
  - <232> (New) Elemental Impurities Chapter - Impact on <381> and <661>
  - <661> Containers—Plastics
  - <XXXX> (New) Extractables Studies Guidance Chapter
  - <XXXX> (New) Leachables Studies Guidance Chapter

USP: First Container Standards

- USP XII (1942) - first container standards - specifically for glass containers used for injectable drug products
  - Chemical Resistance Test
  - Light Transmission Test
  - Water Attack at 121 ° added in USP XV (1955)
- Focus on glass containers used for injectable drug products:
  - Glass was the industry's container material of choice
  - Industry interest in a minimum standard for glass quality
- USP XVII(1965) glass container standard included both parenteral and nonparenteral containers

Biological & Physiochemical Standards

- 1959 USP starts working with orthopedic surgeons to provide plastic standards for implants for internal use
  - Effort was deferred because stakeholders agreed that metallic implants were a bigger concern
- ~1960 USP and NF begin discussion on developing standards for plastics used in connection with pharmaceuticals
- Impetus for discussions:
  - Greater use of plastic material in the pharmaceutical industry
    - Containers
    - Implants
    - Infusion Assemblies
  - Recognition that factors such a plastic composition, processing, cleaning procedures, contacting media and condition of storage could impact patient health

Biological & Physiochemical Standards

- June 25, 1964, in *United States Pharmacopeia Bulletin 49* - a new proposal to become official in *USP XVII (1965)*
  - Section Title: Plastic Materials for Use in Containers and Infusion Assemblies
    - Biological Tests
      - A classification of plastics by means of biological tests - minimum standards to assist in determining biological safety
    - Physical and Chemical Tests
  - Proposed standard was adapted entirely from a PMA collaborative study report
  - Specifications applied to plastics used:
    - As articles physically embedded or implanted in the body
    - In transfusion and infusion assemblies (such as tubing)
    - Containers for drug products intended for parenteral administration

Biological & Physiochemical Standards

- *USP XVII (1965) Biological Tests—Plastics Containers* section was added and made official in the Compendium
  - Biological Tests
    - Six general classes of plastics were set forth (Class I – VI)
    - Systemic Injection Test
    - Intra-cutaneous Test
    - Implantation Test
  - Physical and Chemical Tests; **excluded from *USP XVII (1965)***
    - No specific limits for the tests
- *USP XVIII (1970) Physio-chemical Tests—Plastic Containers section was added and made official in the Compendia*
  - *Nonvolatile Residue*
  - *Residue on Ignition*
  - *Heavy Metals*
  - *Buffering Capacity*

Biological & Physiochemical Standards

- *USP XX (1980) USP reorganized compendia and started using number designations.*
- *New USP General Chapter <660> Containers contained Biological Tests—Plastics and the Physio-chemical Tests—Plastics sections.*

<87> Biological Reactivity, In Vitro

- First appearance in PF 13(5) [Sept.-Oct. 1987]
  - Part of <381> *Elastomeric Closures for Injections*
  - Referenced **ASTM F 895-84** "Standard Test Methods for Agar Diffusion Cell Culture Screening for Cytotoxicity" and
  - **ASTM F 813-01** "Standard Practice for Direct Contact Cell Culture Evaluation of Materials for Medical Devices"

<87> Biological Reactivity, In Vitro

- **F 895-84 is similar procedurally to <87> Agar Diffusion Test**, but with
  - Additional table on Lysis Description
  - Similar criteria for cytotoxic response
- **F 813-01 is similar procedurally to <87> Direct Contact Test** and with similar acceptance criteria.
  - F 813-01 has provision for retesting using twice the number of specimens should one of the two in the first test show cytotoxicity.

<87> Biological Reactivity, In Vitro

- 1988 (Jan.) USP held an Open Conference to explore *In Vitro* toxicity tests as alternatives to the current compendial tests that used animals
  - Focus on elastomers and plastics
- Discussion:
  - Data showed sensitivity of *in vitro* assays and is 97% in agreement with the results of USP *Biological Tests—Plastics*
  - *In vitro* assays exceed the repeatability and reproducibility of the USP *Biological Tests (In Vivo)*
  - *In vitro* methods have been validated for intra-laboratory and inter-laboratory reproducibility
  - ***In vitro* assay could serve as a decision point as to whether or not a sample would be tested in animals**

<87> Biological Reactivity, In Vitro

- New General Chapter Proposed in *PF 15 (3) May-June 1988, "<87> Biological Reactivity Tests, In Vitro*"
  - Determine the biological reactivity of mammalian cell cultures following contact with the elastomeric and other polymeric materials
  - Materials that meet the requirements of <87> would not be subjected to further compendial testing
  - *In Vivo* tests - only by materials previously failed <87> testing
- <87> Chapter Tests: 1) Agar Diffusion Test, 2) Direct Contact Test, 3) Elution Test, and 4) Bacterial Bioluminescence Test
- USP XXII (1990) <87> Biological Reactivity Tests, In vitro added and made official in the Compendia
  - *Excluding the* Bacterial Bioluminescence Test

<88> Biological Reactivity, In Vivo

In parallel with <87> proposals:

- New General Chapter Proposed in *PF 15 (3) May-June 1988*, "<88> Biological Reactivity Tests, *In Vivo*"
- Proposal moved the biological test procedures from *<381> Elastomeric Closure for Injection* and *<661> Containers* to <88>
- USP XXII (1990) <88> Biological Reactivity Tests, *In Vivo* added and made official in the Compendia

<381> Elastomeric Closure for Injection

- 1970 National Formulary included standard, “Rubber Closures for Injections”
  - Biological Test
  - Acute Systemic Toxicity and Intra-cutaneous Reactivity Tests
  - Physicochemical Tests
- 1975, USP purchases the National Formulary
- USP XX (1980) <381> Elastomeric Closure for Injections *added and made official in the Compendia*
  - Same text that appeared in the *1970/1975* National Formulary Rubber Closures for Injections standard

<381> Elastomeric Closure for Injection

- USP XXII (1990) Acute Systemic Toxicity and Intracutaneous Reactivity Tests section was omitted from chapter
- USP XXIII (1995) Biological Test Procedure was removed and reference made to <88> Biological Reactivity Tests, In Vivo
- 1995-2000 revision cycle – Work started to revise chapter, based on stakeholders belief that chapter should have limits/acceptance criteria
- Started process to obtain test data to support the creation of meaningful acceptance criteria

<381> Elastomeric Closure for Injection

- With lack of data to support the creation of meaningful acceptance criteria, the 2000-2005 Expert Committee decided to completely revise chapter so that it would more closely mirror *Ph. Eur. 3.2.9*
  - *Reflect current industry trends*
  - *Minimize the burden of closure testing*
- Proposed revisions appeared in:
  - PF 29 (1) 2003
  - PF 30 (1) 2004
- Independent laboratory study was performed to address issues with PF 30 (1) 2004 proposal

<381> Elastomeric Closure for Injection

- The newly revised chapter appeared in the *Second Supplement to USP 31*, **official date of August 1, 2008**
- Key modifications were:
  - *Establishment of Closure Classifications*
  - *Addition of identification tests*
  - *Elimination of isopropyl alcohol (Extraction solvent C) and drug product vehicle (Extraction solvent B).*
  - *Elimination of closure sample preparation by autoclaving*
  - *Addition of specification limits for the following tests:*
    - *Turbidity [named Appearance of Solution (Turbidity/Opalescence) in revised <381>]*
    - *Reducing Agents (named Reducing Substances in revised <381>)*
    - *Heavy Metals*
    - *pH Change (named Acidity or Alkalinity in revised <381>)*

<381> Elastomeric Closure for Injection

- Additional modifications were:
  - *Addition of the following tests:*
    - *Appearance of Solution (Color)*
    - *Absorbance*
    - *Extractable Zinc*
    - *Ammonium*
    - *Volatile Sulfides*
    - *Functionality Tests:*
      - » *Penetrability*
      - » *Fragmentation*
      - » *Self-sealing Capacity*
  - *Elimination of Total Extractables test*

Agenda

- Past
  - USP: First Container Standards
  - Biological & Physiochemical Standards
  - <87> Biological Reactivity, In Vitro
  - <88> Biological Reactivity, In Vivo
  - <381> Elastomeric Closures for Injections
- Present
  - General Chapter Overview
  - General Chapter —Current Status
  - Importance
- Future
  - <87>/<88> Biological Reactivity, In Vitro/In Vivo
  - <232> (New) Elemental Impurities Chapter (Impact on <381> and <661>)
  - <661> Containers—Plastics
  - <XXXX> (New) Extractables Studies Guidance Chapter
  - <XXXX> (New) Leachables Studies Guidance Chapter

General Chapters Overview

General Chapters can be

- Required (numbered below <1000>)
- Informational (numbered <1xxx>)
- Specific for dietary supplements (numbered <2XXX>)

Required Chapters (Below <1000>)

- When referenced in monographs, are procedures used by the FDA to demonstrate compliance to a specification
- Typically are procedures referenced in multiple monographs
  - Chapter status avoids duplication and simplifies updating
- Typically consist of method and procedure
  - Acceptance criteria – in the General Chapter or the monograph
- Can apply to monographs even if not specifically called out in the monograph
- Tests need to be verified by users for their applications

Informational Chapters (<1xxx>)

- Provide information or guidance
- Are not intended to be enforced by regulatory agencies
  - –Some countries enforce the entire *USP–NF*
  - –FDA reserves the right to enforce if appropriate
- Should be devoid of acceptance criteria to minimize misunderstandings
- May become enforceable if referenced without disclaimer in a monograph or General Chapter numbered below <1000>

General Chapters – Current Status

- Chapters have been
  - Written and updated over many years
  - Under the auspices of many Expert Committees
  - Updated without vision for style and content
- Styles, formats, and information content depend on
  - Committee and USP norms at the time
  - Maturity of technology at time of updating
- Some technology needs to be updated
- We are trying to be very clear regarding what is required versus what is informational

Vision for General Chapters

- Required chapters
  - Current technology
  - Easy to read, understand, execute
  - Clear acceptance criteria – latitude for procedural changes
- Informative chapters
  - Current guidance, no acceptance criteria
  - Context for enforceable chapters
  - Forward looking
  - Relevant to real-world pharmaceutical issues
- All look and read as if edited by one person
- Summarized in *PF* 35(5) Sept/Oct 2009 Stimuli Article

Importance

- Should represent standard industry practice
  - Current technology and acceptance criteria
  - Meaningfully assess quality attributes
- Used across the globe
  - Clear
  - Concise
  - Well-defined acceptance criteria
- Some countries enforce the whole book
  - Some informational chapters contain enforceable sections
  - Confusion, missed expectations, approval delays
- Harmonization – Clear, concise wording is critical

Agenda

- Past
  - USP: First Container Standards
  - Biological & Physiochemical Standards
  - <87> Biological Reactivity, In Vitro
  - <88> Biological Reactivity, In Vivo
  - <381> Elastomeric Closures for Injections
- Present
  - General Chapter Overview
  - General Chapter —Current Status
  - Importance
- Future
  - <87>/<88> Biological Reactivity, In Vitro/In Vivo
  - <232> (New) Elemental Impurities Chapter (Impact on <381> and <661>)
  - <661> Containers—Plastics
  - <XXXX> (New) Extractables Studies Guidance Chapter
  - <XXXX> (New) Leachables Studies Guidance Chapter

Toxicology

- <87>/<88> Biological Reactivity, In Vitro/In Vivo – no revision activity in the last 15 years - no comments were received by USP

- **Major Limitations**
  - Tests are only of an acute nature
  - Short term effects not addressed
  - Slanted towards devices

- A revision to <88> to include subcutaneous rat implantation for materials with physical characteristics unsuitable for routine intramuscular implantation - proposal currently in PF 36(6), Nov-Dec 2010 issue

- The USP Toxicology EC is currently reviewing both chapters to determine their strengths, weaknesses and toxicological relevance and propose appropriate revisions

<232> (New) Elemental Impurities

Heavy Metals <231>

- Difficulties in reproducibility
  - Monitor solutions, standards, recovery issues
- Difficulties with reagents – safety issues
  - All procedures generate H_2S; thioacetamide not allowed in California and several European countries
- Nondiscriminatory screening test
  - Not element specific
  - Sensitivity varies by element
  - Only a few elements respond at required sensitivities
- Visual comparison test
  - Limits based on visual acuity, not toxicology

Elements – *Elemental Impurities-Limits* <232>

- As, Pb, Cd, Hg
- 12 of 14 Elements in EMEA Guidance
  - Zinc and iron excluded - not toxic at levels relevant in pharmaceuticals
- Elements to be limited if added or if there is potential they can be added inadvertently (e.g., through the manufacturing process, leaching from packaging)
- All limits toxicologically based
- ICH Q3D may broaden number of metals considered

<232> (New) Elemental Impurities- Impact

- Once <232> is official, there likely will be a scheduled removal of <231> Heavy Metals from the Compendia
- <232> Elemental Impurities - limits is meant for finished drug products, not packaging materials
- Removal of <231> Heavy Metals from the Compendia it will have an impact on following packaging chapters
  - <381> Elastomeric Closures for Injections
  - <661> Containers-Plastics
  - <660> Containers-Glass

Packaging, Storage and Distribution

- Develop elemental impurity specifications for core packaging chapters
  - <381> Elastomeric Closures for Injections
  - <660> Containers-Glass
  - <661> Containers-Plastics
- Major revision to <661> Containers-Plastics
  - A single chapter or series of chapters for the major classes of materials used in pharmaceutical packaging.
  - Include tests and specifications that are relevant to a particular material, and reference core test methods and requirements common to all the materials.

Packaging, Storage and Distribution

- <XXXX> Extraction Studies
  - **Guidelines for design and conduct of extractions studies**
    - Delineate and justify best practices for the design and conduct of extraction studies, including the generation of the extract and its analysis.
    - Strive for commonality and consensus across the varied pharmaceutical dosage forms, but properly address the unique nature of the many varied dosage forms.
  - New Chapter projected to be published in PF in early 2012
- <XXXX> Leachable Studies (Toxicological Safety Assessment)
  - PSD EC believe it is premature to move forward with a chapter.
  - PSD EC is monitoring the progress of many efforts currently underway to identify the proper starting point for this activity.

Future Directions

- Future directions depend on outcomes of workshops like this one
- What are the gaps in extractables/leachable guidelines?
- USP Expert Panels – Can they pull together the information in a way that provides clear guidelines to those doing the experiments and making product development decisions?
- Final USP directions rest what the industry needs and the EP's decisions on how USP can help

U.S. PHARMACOPEIA
The Standard of Quality℠

Thank You