Widescale Adoption of Single-use Systems: Challenges Ahead from the Regulators', Suppliers' and End-Users' Perspectives

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Challenges - Risks of Single-use Systems

- Physical Integrity
  - Ruptures, Leaks
- Microbial
  - Bioburden, Sterility, Barrier
- Particulates
  - Visible, Sub-visible
- Chemical
  - Leachables, Adsorption
  - Protein reactivity
- Biological
  - Systemic toxicity
  - Immunoreactivity
  - Cytotoxicity, Growth effects
- Supply
  - On-time delivery
- Consistency
  - Reliability
  - Quality, documentation
- Regulatory
  - Data packages
  - Risk assessment
- Application
  - Upstream
  - Downstream
  - Formulation and Filling

Regulations and Guidance

FDA Guidance for Industry: CGMP for Phase 1 Investigational Drugs (July, 2008)

…technologies … that can facilitate conformance with CGMP and streamline product development include:

- Use of disposable equipment and process aids to reduce cleaning burden and chances of contamination
- To the extent possible, dedicated equipment and or disposable parts (e.g. tubing) is recommended

FDA Guidance for Industry: CGMP for Phase 1 Investigational Drugs (July, 2008)

- Use of commercial, prepackaged materials (e.g., Water For Injection (WFI), pre-sterilized containers and closures) to eliminate the need for additional equipment or for demonstrating CGMP control of existing equipment
- Use of closed process equipment (i.e., the phase 1 investigational drug is not exposed to the environment during processing) to alleviate the need for stricter room classification for air quality

Industry References

- BPSA Component Quality Test Reference Matrices
  - Published 2007
  - Available at www.bpsalliance.org
  - Supplier consensus quality tests
    - Biocontainers
    - Filters
    - Tubing
    - Connectors
  - Update in development - pending 2014
    - Sensors
    - Chromatography

Industry References

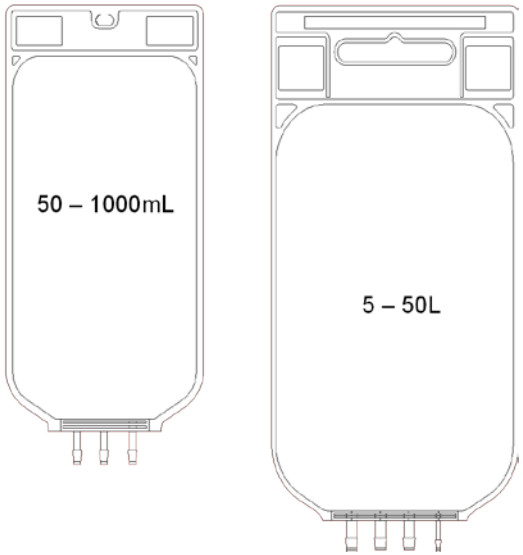
- PDA Technical Report on Single-use Systems
  - Publication pending 2014
  - User, Supplier and FDA consensus
  - Quality by Design approach

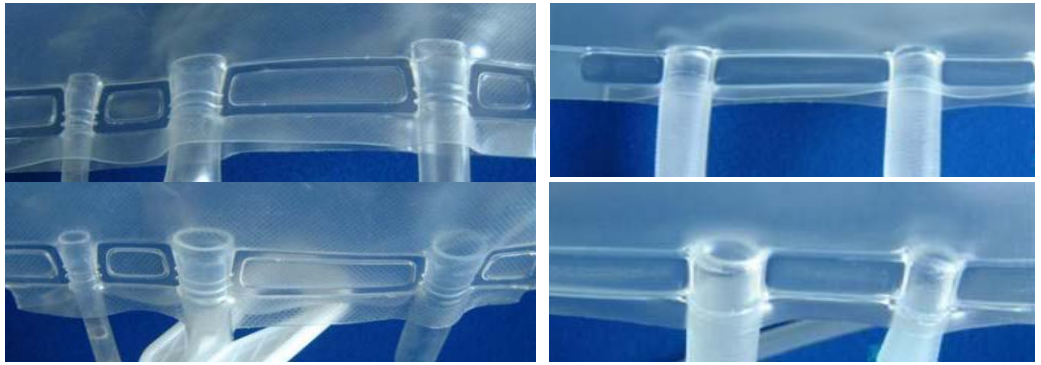
  - When published:
    - 30 day free download to PDA members
    - Available at www.pda.org

Physical Risk Qualification

Physical Risks – Design Improvements

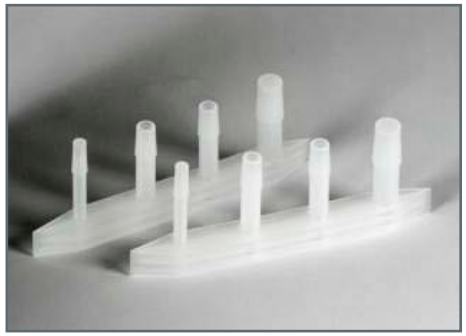
- Continuous seams
- Molded fitting assemblies (boat design)





Sealed tube connectors

Molded boat connectors



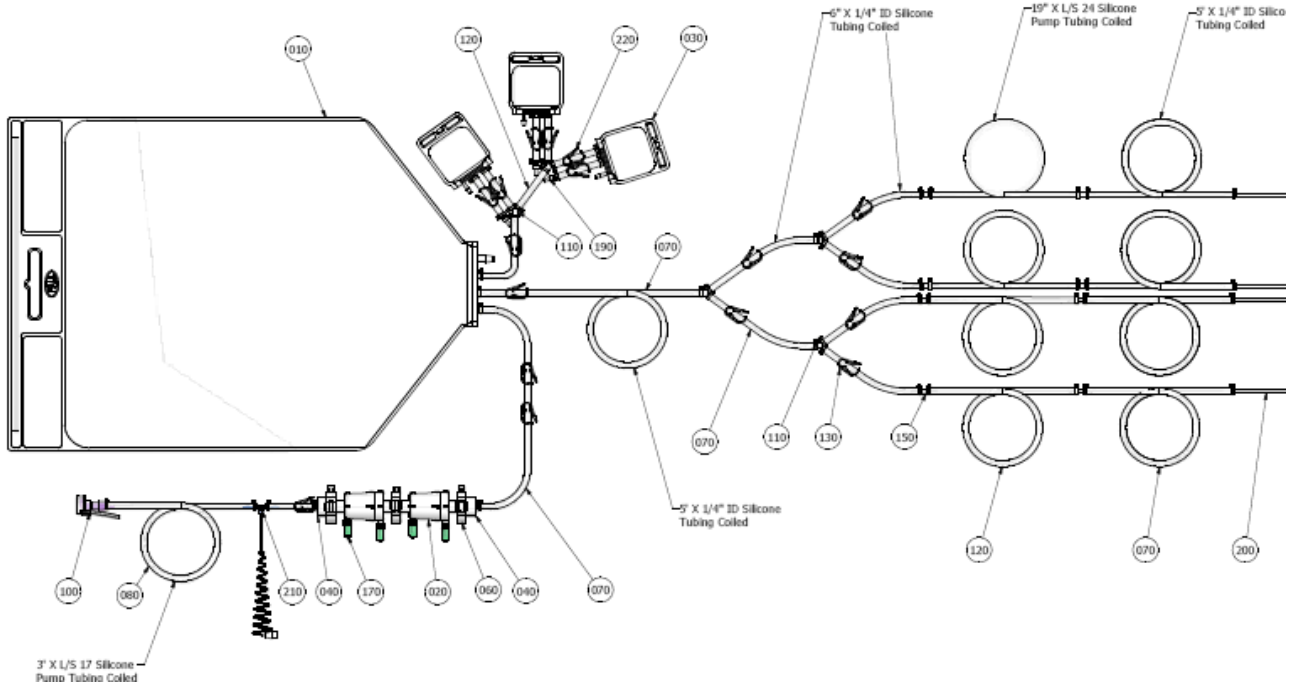
Physical Risks – Design Improvements

- 2D totes eliminate hanging stresses
- Front-loaded 3D totes + self-filling 3D biocontainers reduce handling, eliminate stress cracking, pulling
- Multi-operation platforms reduce system stresses

Particulates Risk Qualification

Particle Risks in Single-use Systems

- Potential to contaminate final dosage and cause harm to patients
- Post-filtration filling systems
- Aseptic processes without inline filtration



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Potential Sources of Particles in SUS

- Resin hoppers / bins must clean
- Components
  - Filters, biocontainers, connectors, tubing
- Biocontainer and system assembly
  - 2D and 3D biocontainer manufacturing
  - Tube cutting
  - Hosebarb fitting
- Environment
  - Operator gowning and training
  - Mfrg & assembly air quality

Reduction of Particulate Risks

- "Non-particle-releasing" filters
  - Flushed in manufacturing
- Optically clear biocontainer films
- Multilayer film extrusion
- Cleanroom assembly
  - ISO 7 (Class 10,000 / Grade C)

Visible Particle Qualification

- "Essentially free" is undefined
- SUS cannot be "inspected" when empty
  - QbD engineering of component mfr and assembly
  - Supplier operator "surveillance" as final check
  - "Worst case" surrogate system for periodic monitoring
- User "surveillance pre/post filling
  - Significance of single visible particle in bulk?
  - Risk of being missed during bulk or final inspection?

Particle Limits - Compendial Tests

- Visible Particles in Drug/Vaccine Products
  - USP <1>: Injectables
  - “essentially free of visible particles”
- Subvisible (microscopic) Particles
  - USP <788> Particulate Matter in Injections
  - Methods, limits for >10-25 µm and >25 µm particles
- SUS Particle Testing
  - Apply USP limits (to rinse effluents)
  - No industry guides, standards or regulatory guidance

Industry Collaboration

- BPSA Suppler/User Task Group
- BPSA SUS Particulates Guide
- Publication pending 2014

Chemical and Biological Risk Qualification

Chemicals in Polymer Formulations

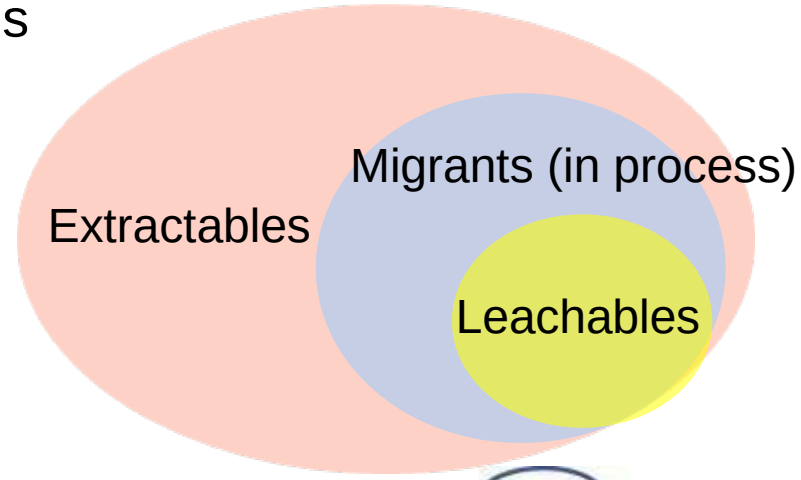
- Polymers
  - Oligomers
  - Unreacted monomers
- Additives
  - Polymerization agents, pore formers
  - Stabilizers, antioxidants,
  - Anti-static agents
  - Processing / extrusion / mold release agents
  - Colorants

Materials/Component Biological Safety

- Quality by Design – Material Prequalification
  - USP <88> Biological Reactivity Tests, *in vivo*, for Class VI plastics
    - Extractions in saline, ethanol, polyethylene glycol, vegetable oil
    - Systemic toxicity evaluations
  - USP <87> Biological Reactivity, *in vitro*
    - MEM cytotoxicity
- Post-sterilization Component Qualification
  - Autoclave at >121-135 ºC or Gamma to 50 kGy
  - Repeat compendial tests on mfr'd/treated materials

Leachables, Migrants, Extractables

- Chemicals that can migrate into (dissolve in) process fluids or product
  - Leachables – in final product dosage
  - Migrants (“in-process leachables”) – in process fluids
  - Migrants (per FDA) – leachables from external sources
  - Extractables – potential leachables
    - Exaggerated dissolution conditions
      - Stronger solvents,
      - Higher temperatures
    - Aid in predicting in “in-process” and final dosage leachables



Industry Standardization

- BPSA Extractables Guides (2008, 2010)
  - Consensus of suppliers and independent labs
  - Reviewed with FDA and users
  - Many successful approved applications
  - Risk-based approach
    - Water and ethanol extractions
    - Broad analyses (e.g. FTIR, LC-MS, GC-MS, ICP-MS)
  - Available at www.bpsalliance.org

Industry Standardization

- ASME-BPE SU Extractables Standard (Draft)
  - Consensus of member users and suppliers
  - 2014 draft broader than current 2012 section
    - Defines extractables, leachables, and “bracketed leachables”
    - Recommended component extraction conditions in “Non-mandatory” Appendix
      - » Water or alcohol for polar
      - » Hexane or toluene for non-polar
      - » Samples, extraction conditions and analytical methods not specified

Industry Standardization

- BPOG Proposal / BPSA Collaboration
  - BPOG user expectations for supplier data
    - Multiple extraction solvents
    - Sample size/area, extraction volume
    - Extraction conditions (temperature, times, dynamics)
    - Analytical methods
  - BPSA counter proposal from suppliers, users
    - Agreement in principle
    - Technical justifications, exceptions and cost concerns
    - How will results be used?
    - Negotiations in progress

Industry Standardization

- USP Standards and Regulators
  - Revision of USP <661> Containers – Plastic
  - Proposed Inclusions:
    - 661.1 Plastic Materials of Construction
    - 661.2 Plastic Packaging Systems for Pharmaceutical Use
    - 661.3 Manufacturing Systems
  - New General Chapters
    - 1663 Extractables Testing
    - 1664 Leachables Testing
    - 1665 Toxicity Assessment of Leachables

USP <661> Containers - Plastic

- Standards for plastic materials for containers for solid or liquid oral dosage forms.
  - Applicable to Polyethylene, Polypropylene, and Polyethylene Terephthalate (polyester) containers
- No requirement to test if already included in Indirect Food Additives GRAS (21 CFR)

- Physiochemical tests
  - IR and DSC (differential scanning calorimetry)
  - NVR, Residue on Ignition, Heavy Metals
- Biological Safety tests
  - USP <87> Biological Reactivity Test, In Vitro

Original USP <661> Limitations

- Test methods not precise or a complete indicator/predictors
  - Safety & quality of packaging,
  - Not used for administration systems
  - Not intended for SU manufacturing suites
- Test methods need modernization, harmonization
  - e.g Heavy metals tests outdated for analysis of elemental impurities
- Chapters were limited to a few plastics
- Chapters specific to oral dosage forms

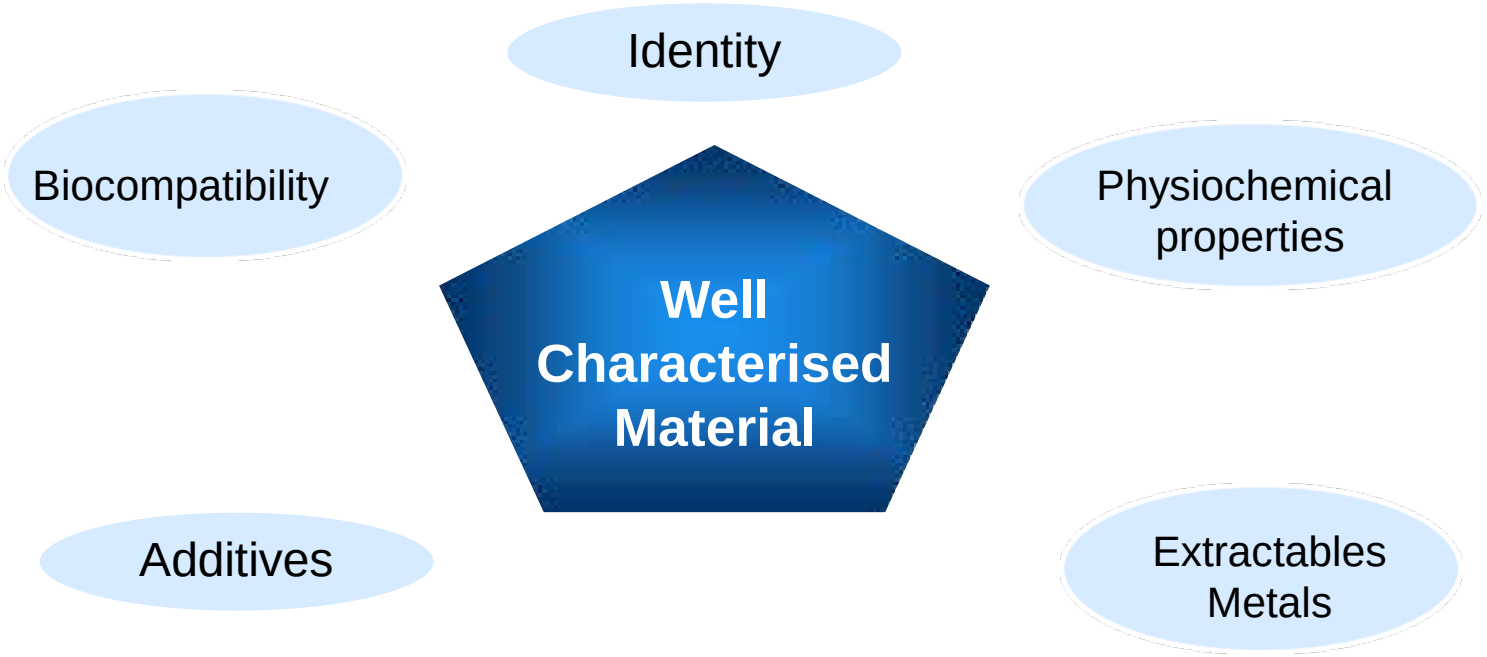
Revised <661> Plastic Packaging Systems and their Materials of Construction

- Describes Three Phases of Assessment:
  - Material Screening
    - Identify materials suitable for use
    - Characterize materials to evaluate ingredients as probable extractables and tentative leachables
  - System Assessment
    - Controlled extraction or ”worst case” simulation study to determination of extent that extractables may become probable leachables
  - Product Assessment
    - Actual case measurement of confirmed leachables

Proposed Amendment <661.1>

<661.1> Plastic Material of Construction

A material is deemed well characterised by establishing:



Proposed Amendment <661.2>

- <661.2> Plastic Packaging Systems for Pharmaceutical Use
  - Test methods and standards for packaging systems
  - Individual materials of construction tested for extracted metals
  - Regulatory expectations to be met, the packaging needs to be appropriately tested
  - Drug applicant to provide evidence of safety
    - » Chemical testing refers to E & L testing
    - » Toxicological Assessment

Proposed Changes

- Chemical testing is essential
  - Indicator of safety/quality but no guarantee
- Orthogonal approach required
  - Biocompatibility: USP <87> will remain part of <661>
- Physiochemical tests – no direct evidence of safety or quality
  - Certain tests indicative of quality impact
  - TOC reflects total amount of extracted organic compounds
  - UV indicates of chemical nature of organic extractables
- Historical tests – no longer applicable
  - NVR, residue on ignition testing

Elementary Impurities

- Replacement of Heavy Metals test
  - Based on sulfide precipitation
  - New methods of choice: Atomic Absorption spectroscopy (AA) and inductively coupled plasma spectrometry (ICP-MS)
- Generation of test samples
  - Should not dissolve under conditions of use
  - Appropriate sample prep process for assessing metal extractables/elemental impurities from packaging materials is extraction

- PhEur, USP and ICH are developing new chapters
  - Harmonisation with specification listed for relevant metal in *Ph.Eur*

Proposed Chapter <1663>

- Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems

- Two aspects
  - Generating the extract
  - Characterising the extract

- Stimulus document:
  - Indicates not possible to anticipate every situation
  - Does not contain required analytical procedures
  - No mandatory extractables specifications and/or acceptance criteria

Proposed Chapter <1663> cont'd

- Generating the test extracts
  - Identifying chemical nature of the extracting medium
  - Considering extraction time and temp
  - Determining extraction stoichiometry
  - Establish the mechanism of extraction-extraction technique

- Characterising the test extracts
  - Processes involved extract characterisation
    - Discovery
    - Identification
    - Quantification

Proposed Chapter <1664>

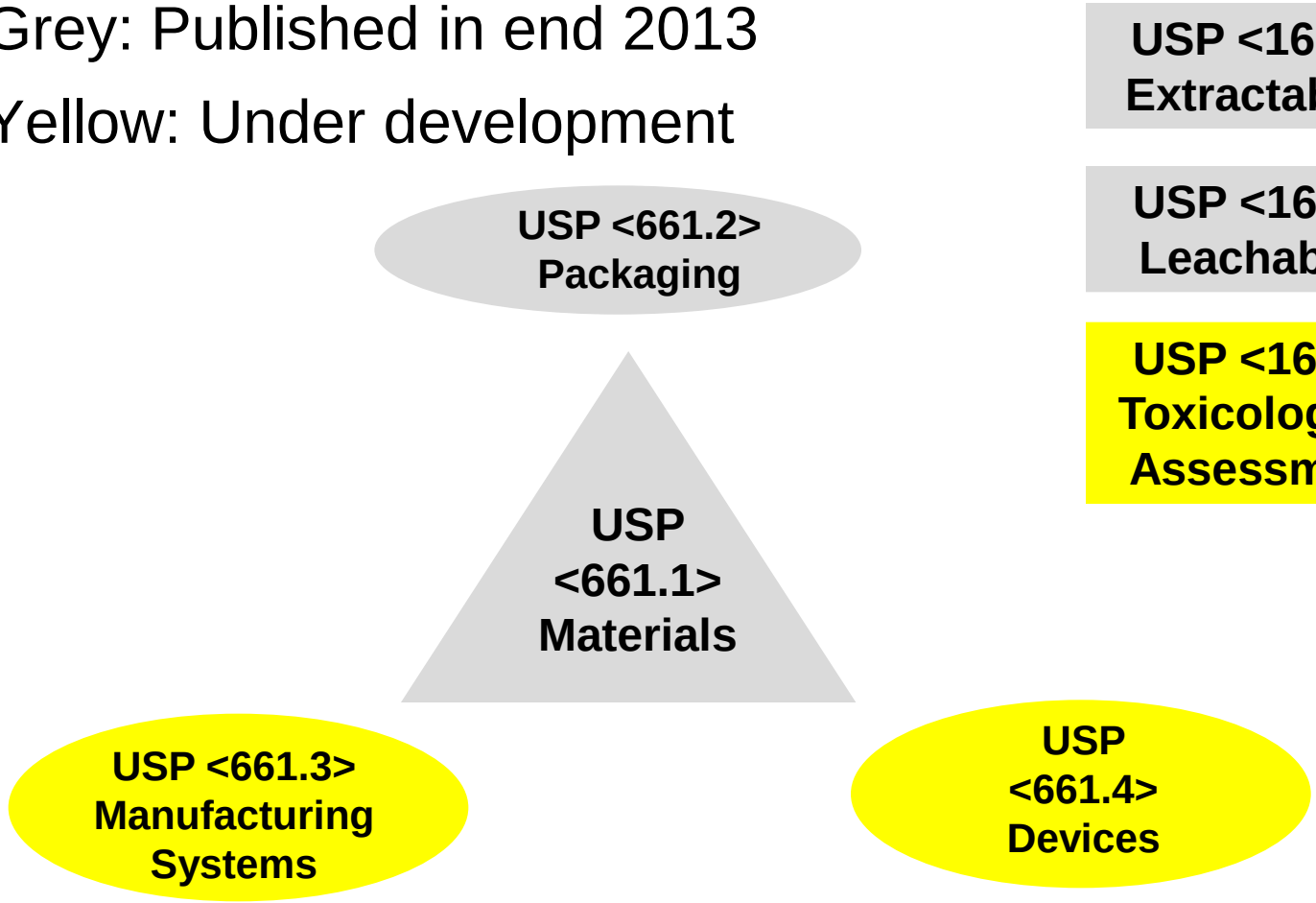
- Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems
  - Best practices recommendations
  - Articles tested can be complete system or separate components
  - Drug product sample preparation for leachables analysis
  - Simulation studies
    - Elemental impurities
    - Leachables where not analytically feasible

Proposed <661> Amendments and USP Chapter <1665>

- <661.3> Manufacturing Systems
  - Test methods and standards for single-use materials, components and systems
  - Pending BPOG/BPSA Consensus
- <661.4> Devices
  - Test methods and standards for devices used with combination products
- <1665> Toxicological Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems

Universe of USP Chapters

- Grey: Published in end 2013
- Yellow: Under development

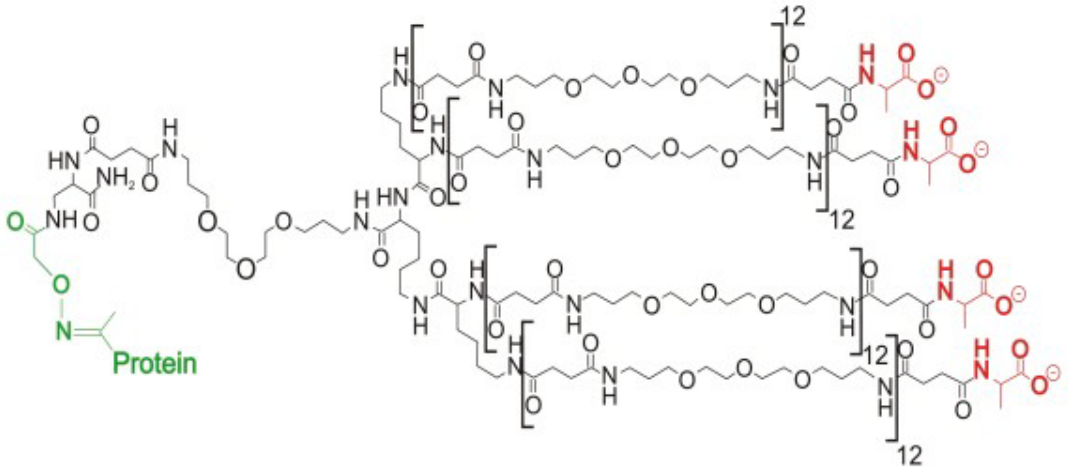


Industry Standards

- ICH Q3D Guideline for Elemental Impurities (EIs) in Drug Products
  - Catalysts (added to materials intentionally)
  - Contaminants (leached from equipment, containers)
  - Present in raw materials
  - No therapeutic benefit to the patient
  - Controlled in drug product to acceptable limits

ICH Q3D Scope

- Applies to drug products
  - New finished drug products and new drug products employing existing drug substances
  - Includes:
    - Recombinant/non-recombinant cell culture expressions
    - Proteins
    - Polypeptides
    - Polynucleotides
    - Oligosaccharides



ICH Q3D not applicable for ….

- Herbal products
- Radiopharmaceuticals
- DNA products
- Whole blood
- Vaccines
- Cell metabolites
- Crude products of animal or plant origin

ICH Q3D Structure

- Three components:
  - Evaluation of toxicity data for potential elemental impurities
  - Establishment of a Permitted Daily Exposure (PDE) for each element of toxicological concern
  - Development of controls to limit the inclusion of elemental impurities in drug products to levels at or below the PDE

Classifications of Elemental Impurities

Classification	Description	Include in Risk Assessment?
Class 1	Significantly toxic across all routes of administration	Yes
Class 2	Toxic to a greater or lesser extent based on route of administration	Class 2A – Yes Class 2B – Yes only if intentionally added
Class 3	Impurities with relatively low toxicity (high PDEs) by the oral route of administration but require consideration in the risk assessment for other routes of administration	Dependent upon route of administration
Class 4	Elemental impurities have been evaluated but for which a PDE has not been established due to their low inherent toxicity and/or regional regulations	No

Assessment and Control of Elemental Impurities in Drug Products

- Four-step process:
  - Identify:
    - Qualify known and pot'l sources of Eis in the drug prod.
  - Analyze:
    - Determine the probability of observance of a particular EI
  - Evaluate:
    - Compare the observed or predicted levels of EIs with the established PDEs
  - Control:
    - Document and implement a control strategy to limit EIs in the drug product

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Quality by Design in Materials for Single-use Systems

Supplier Materials Selection

- Quality by Design
  - Reduce risk of undesirable migrants and leachables
- Avoid unsafe Extractables / Leachables
  - No rubbers (only Pt-cured silicone gaskets and o-rings used)
  - No latex, no polyvinyl chloride (no phthalates), BPA
  - No known genotoxicants, no Class 1 solvents
  - Animal-free or BSE/TSE statements
  - pH resistant polymers for pH adjusters, buffer prep,' e.g. polypropylene and polyethersulfone (PES)
- Supplier Disallowed and Controlled Substances
  - e.g., www.pall.com/pdfs/About-Pall/E962.pdf

Bioburden Control and Sterilization Qualification

Bioburden Control and Sterlization

- Suppliers
  - Controlled clean manufacturing
  - Bioburden monitoring
  - Gamma irradiation for microbial control
  - Gamma sterilization validation
  - Dose mapping
  - Lot certification
  - Periodic dose audits

Bioburden Control and Sterlization

- Users
  - Reference Documentation
    - Gamma sterilization validation report
    - Dose mapping report
    - Lot certification
    - Periodic dose audit report
  - Audit supplier
    - Ref: Biogen Idec FDA 483 08/02/2013

1) There is no assurance that the firm always challenges the validity of all testing results provided in container-supplier's certificates of analysis as part of supplier qualification procedures. [redacted] (b) (4) bulk bags, used as the container closure system of Tysabri API, are received with certificate of analyses indicating that the bags are sterile and endotoxin free; however, these results have never been challenged and/or verified by the firm.

Sterilization Standards

- ANSI/AAMI/ISO 11137:2006
  - Sterilization of health care products - Radiation
  - (Parts 1 – 3)
- AAMI TIR33:2005 (supplement)
  - Sterilization of health care products - Radiation
  - Substantiation of a selected sterilization dose - Method VDmax
- Single-use Industry Collaboration
  - BPSA Guide published 2008
  - Application of standards to single-use systems
  - Available at www.bpsalliance.org

Quality and Supply Chain Security

Consistency Risk - Change Control

- Supplier Audits
  - Raw materials and components
  - Manufacturing controls
  - Quality system
- Quality Agreements
  - Raw materials and component suppliers
  - Supplier Change Notifications
- Industry Collaboration
  - BPSA Quality Agreement Template
  - In draft, target 2014 publication

BPSA Quality Agreement Template

- Objectives
  - Accelerate the formation and approval of quality agreements between vendors and users
  - Establish more consistent expectations for quality systems, change management, notification, etc.
  - Establish consistent performance criteria expectations
  - Improve communications between parties
  - Enhance the quality (predictable performance) of single-use products

BPSA Quality Agreement Template

- Consensus Development
  - Supplier Quality Agreement Templates
  - User Quality Agreement Templates
  - Industry Quality Agreement Templates
    - SOCMA, APEC - Bulk Pharm Chemicals, API
    - IPAC-RS – OINDP mfrs, developers and materials suppliers
  - FDA Guidelines for Biological CMOs/Sponsors

Widescale Adoption of Single-use Systems

What are the Challenges Ahead?

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