Industry Perspective concerning USP Packaging Chapter Series:
<381>, <660>, <661>, <665>

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Purpose

- To present the perspective of the pharmaceutical industry with respect to the following revised General Chapters
  - Official Stage: Major Revisions
    - <661>/<661.1>/<661.2>/<1661> (primary focus)
  - Proposal Stage: Major Revisions/New Chapters
    - <381>
    - <360>/<1660>
    - <665>/<1665>

- Create a collaborative dialog between industry, FDA, & USP
Presentation will not focus on many technical issues but primarily on practical difficulties with implementation primarily with <661> chapter series

- Subject Matter/Technical experts are in the room and on the web-ex to facilitate those discussions
- Industry asked to deliver a P/NP presentation to focus on <661> series
Industry Difficulties

- Limited Industry resources to focus on numerous USP changes
  (USP Chapter Revisions)

- Too many—Too fast

Senator Susan Collins (ME), “Sweeping reforms to our health care system and to Medicaid can't be done well in a compressed time frame, especially when the actual bill is a moving target”
Recommendations for all chapters

- Publish highly impactful revisions in PF
- Develop standards with clearly written requirements
  - Avoid cross-referencing of general chapters
- Develop feasible implementation timelines with Industry and FDA
- Develop future general chapter standards utilizing...
  - “Expanded” Advisory/Expert Panel
    - Regulatory
    - Site Quality Laboratory Personnel
    - Change Control & Compendial SMEs
Official Stage:
Major Revisions/New Chapters
PLASTIC PACKAGING SYSTEMS AND THEIR MATERIALS OF CONSTRUCTION

PLASTIC MATERIALS OF CONSTRUCTION

EVALUATION OF PLASTIC PACKAGING SYSTEMS AND THEIR MATERIALS OF CONSTRUCTION WITH RESPECT TO THEIR USERSAFETY IMPACT
USP Actions beneficial to Industry

- Discussions with Industry
- Technical Revisions requested by industry
- Inclusion of a risk based approach
Could risk industry’s ability to:

- Provide medicines
  - Potential compliance difficulties for approved materials
  - Significant implementation endeavor for global companies

- Provide monograph submissions and reference standards
  - Reduction in resources focused on these activities
    - Human, Internal labs, CROs, Compendial, Regulatory, etc.
Background Information
Industry Pharmacopeial Revision Implementation Process
Multiple vendor contact meetings
Multiple meetings to plan for change
Above-Site Groups
  ▪ (SMEs)
Regulatory Groups
  ▪ (US and Ex-US)
  ▪ Review of 150+ filings
Change Control/Documentation
  ▪ Review of numerous documents used at global sites
  ▪ Review of Site documents – worksheets, LIMS, etc.
Manufacturing/Testing site
  ▪ Verification Testing/Assessment per dosage form
  ▪ Review of LIMS
  ▪ Review of testing documentation
  ▪ Review of SOPs
Change Control Impact Implementation Execution

- **Above-Site Groups**
  - (SMEs)

- **Regulatory Filings**
  - (US and Ex-US)
  - 150+ filing updates
  - Cost for filing changes
  - As long as 5 years to approve

- **Change Control/Documentation**
  - Numerous documents used at global sites
  - Site documents – worksheets, LIMS, SOPs, etc.

- **Testing at manufacturing sites**
TIMELINE
History of USP Plastics Packaging General Chapter Series

PF 39.5
<661> = Major revisions. <6611> and <6612> & <6613> proposed

USP 39
<661> chapter revisions official with exemption clause.

FAQ Document
FAQ documented posted for clarification

PF 42.3
<6613> introduced

PF 42.4
Additional revisions to <6611> & <6612>

USP 41
Additional revisions to the chapter will be posted

2013

2015

USP PF 40.5 & 40.6
PF 40.5 = USP 39.5 revisions cancelled & replaced. PF 40.6 = <1661> introduced.

2016

Revision Bulletin
Removed the exemption clause & postponed revisions until 2020.

PF 43.3
<6613> replaced by <665> (expanded scope). <1665> replaced <16613>.

2017

2018
Difficulties Experienced in Industry

- Condensed Implementation Timeline not feasible
  - Impact of <661> Exemption Removal
  - Clarification of Chapter Requirements
  - Cross referencing chapters
  - Currently approved packaging impact
Difficulties Experienced by Industry

**Implementation Timeline**

- Industry was not consulted prior to publishing the revised timeline in the 2017 Revision Bulletin

- USP <661> Implementation Timeline is not feasible based on other competing USP revision mechanisms/initiatives
  - <232>/<233>, <660>/<1660>, <381>/<382>, <857>/<856>, <665>/<1665>
  - USP publications (3 publications, bimonthly (now monthly) web postings, notices, website updates)
Difficulties Experienced by Industry

Implementation Timeline

- Additional revisions essentially reset timeline
  - “Moving Targets” eliminate opportunity for early implementation

- Current implementation timeline would be significant challenge for both global and national companies with large and small product portfolios
Difficulties Experienced by Industry

Exemption Removal & Timeline

- No indication that exemption was temporary/being removed
  - Companies may have developed USP 39 implementation strategy using Exemption

- Revised implementation timeline assigned with a limited amount stakeholder/industry input
  - How was the three year timeline determined?
  - Impacted by any potential assessment testing failures with approved/marketed products

- Would have been better proposed in a PF publication
  - Would have allowed both industry and FDA appropriate time to give appropriate input concerning implementation activities
Difficulties Experienced by Industry

Chapter Clarification

- Standard as written is understood by Expert Committee and Subject Matter Experts (SMEs) not necessarily the average user
  - Risk-based approach language is not clearly stated/understood
  - Risk-based approach assumes legacy products have data to meet <661>

- Scope – clarification needed
  - Chapter applicability based on product type

- FAQs/verbal clarification are useful but are not source documents. They are not official text, and users may not be aware or able to find the FAQs.
  - Use of FAQs highlight the need for chapter clarification
Simultaneously working on series of chapters that are related or contain cross references creates confusion

- Revisions to <661.1> impacts implementation work for <665> that list <661.1> references

- <661.3> was changed to <665>
  - Scope no longer included plastic packaging.
  - <661.1> requirements referenced in <665> may not be suitable (different conditions of use).
Industry Recommendations – <661> Chapter Series

- While these recommendations were generated for <661> series:
  - They can be applied to other major general chapter changes as well
  - Continue collaboration between industry USP, FDA, and industry to prevent difficulties in the future
Industry Recommendations

<661> Chapter Series

- Consideration of other existing regulations to avoid possibility of divergent requirements

- For future changes, earlier engagement via clearly written Stimuli Articles, PF, Expert Panels, Prospectus, etc.

- Use of a “phased in” approach with the Official Date extension for different dosage forms
  - Phases and due dates to be worked out by USP, FDA, and Industry

- Extension of Official Date working with Industry & FDA (lesson learned from <232/233>)
  - Including consideration for potential difficulties during assessment verification
Industry Recommendations
<661> Chapter Series

- Addition of clarification language into chapter
  - FAQs while useful are not source documents
  - Allowance for Risk based approach should be clearly defined
  - Standards should be written so that the average user understands

- Consideration of creation of expanded advisory/expert panel with industry representation

- Changes should be listed in the PF
  - Use of rapid implementation mechanisms should only be used in appropriate cases (urgent safety and compliance needs)

- Avoid major simultaneous revisions to multiple, broadly impactful chapters
Proposal Stage: Major Revisions/New Chapters
ELASTOMERIC CLOSURES USED IN INJECTABLE PHARMACEUTICAL PACKAGING/ DELIVERY SYSTEMS
Comments received include:

- **Potential for Divergence from ICH Q3D**
  - List of extractable elements in the general chapter are not aligned with ICH Q3D Classes 1 through 3.

- **Need for Clarification**
  - Extraction instructions could be clarified to assist users
CONTAINERS—GLASS

EVALUATION OF THE INNER SURFACE DURABILITY OF GLASS CONTAINERS
Comments include:

- Consideration to define Type I glass based on performance rather than composition
  - Allows for new and additional types of glass that could be superior to borosilicate
  - Allows testing for stability of material’s performance providing enhanced safety benefit

- Consideration for other testing methodologies to better determine performance

- Consideration of extension of Official Date
  - Per USP Webcast: <660> updates will be published in 2018/2019
POLYMERIC COMPONENTS AND SYSTEMS USED IN THE MANUFACTURING OF PHARMACEUTICAL AND BIOPHARMACEUTICAL DRUG PRODUCTS

PLASTIC COMPONENTS AND SYSTEMS USED TO MANUFACTURE PHARMACEUTICAL DRUG PRODUCTS
Industry Recommendations

Consideration of the pace of highly impactful chapter revisions versus industry capability

Consideration to remove vaccine and biological products from chapter scope
- Most vaccine & biological ingredients are manufactured around a neutral pH Unlikely to extract any material out of plastic.

Relocate <665> information to <1665> listing risk factors for the extreme cases that may cause extractables/leachables

Consideration of Official Date Extension

Consideration to remove <661.1> chapter references
Recommendations for all chapters

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Thank you so much