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>
    - <660>/<1660>
    - <665>/<1665>
- Create a collaborative dialog between industry, FDA, & USP

Presentation Level - Setting

- 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

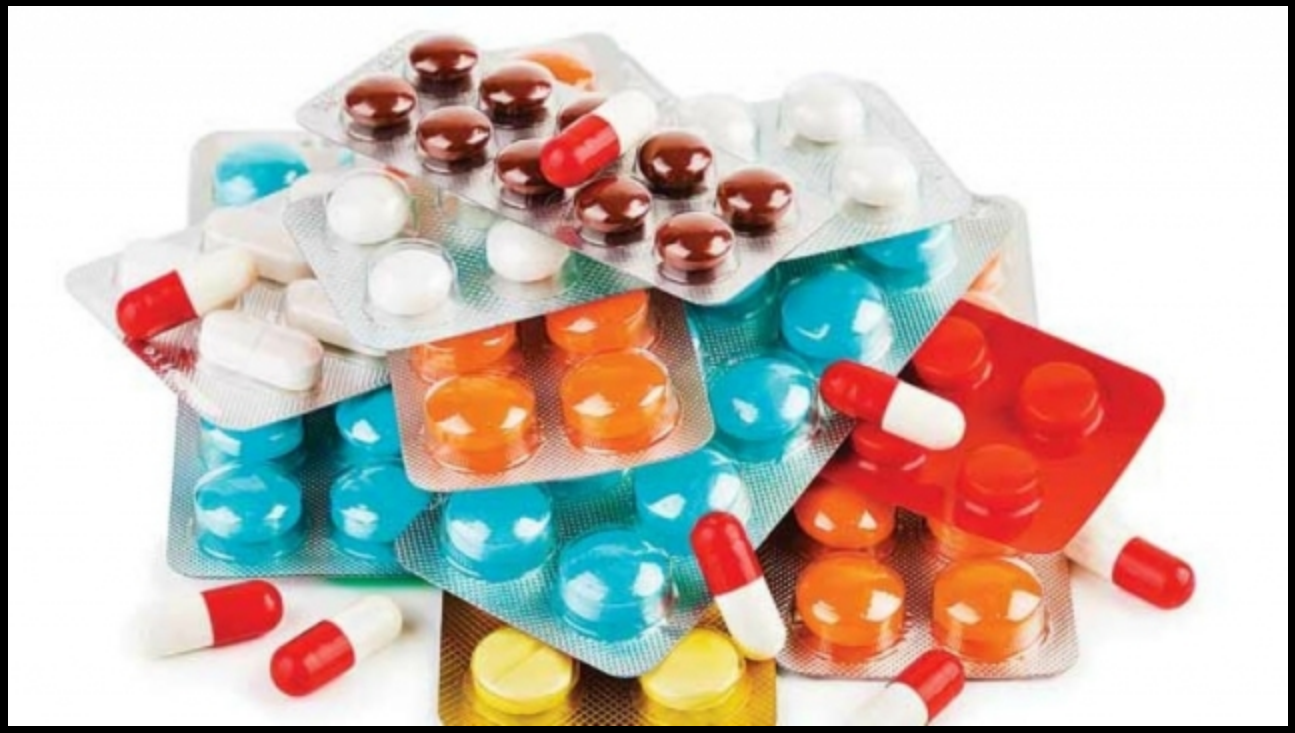
Senator Susan Collins (ME), "Sweeping reforms to our health care system and to Medicaid can't be done well in a compressed time frame, especially when the actual bill is a moving target"

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

<661>/<1661>
<661.1>
<661.2>



<661>, <661.1>, <661.2>, <1661>

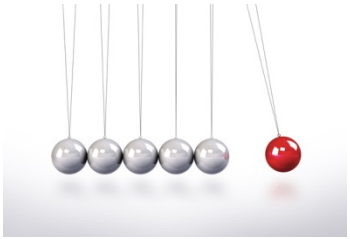
<661> PLASTIC PACKAGING SYSTEMS AND THEIR MATERIALS OF CONSTRUCTION
<661.1> PLASTIC MATERIALS OF CONSTRUCTION
<661.2> PLASTIC MATERIALS OF CONSTRUCTION
<1661> EVALUATION OF PLASTIC PACKAGING SYSTEMS AND THEIR MATERIALS OF CONSTRUCTION WITH RESPECT TO THEIR USERSAFETY IMPACT

USP Actions beneficial to Industry

- Discussions with Industry
- Technical Revisions requested by industry
- Inclusion of a risk based approach

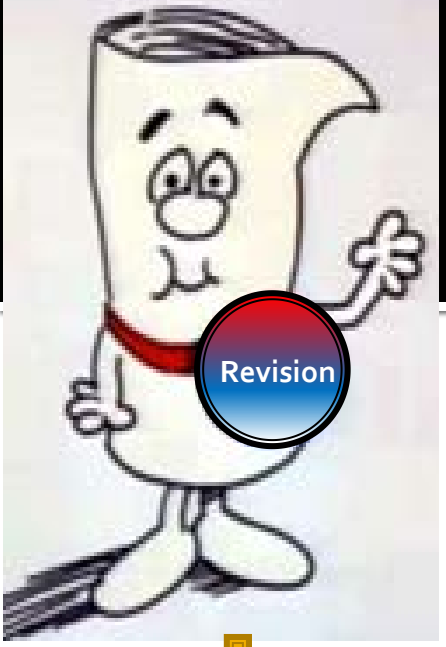
Potential Unintended Consequences

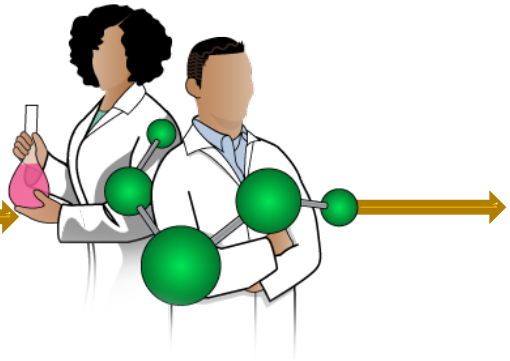
- Could risk industry's ability to:
  - Provide medicines
    - Potential compliance difficulties for approved materials
    - Significant implementation endeavor for global companies
  - Provide monograph submissions and reference standards
    - Reduction in resources focused on these activities
      - Human, Internal labs, CROs, Compendial, Regulatory, etc.

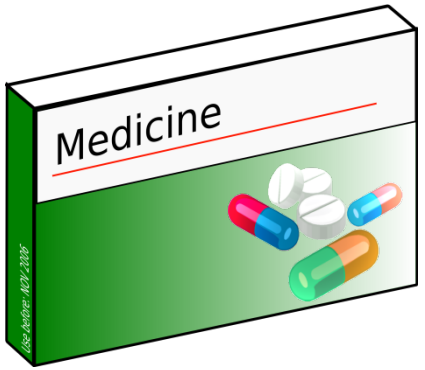


Background Information

Industry Pharmacopeial Revision Implementation Process



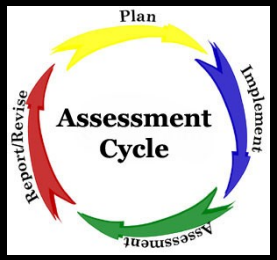




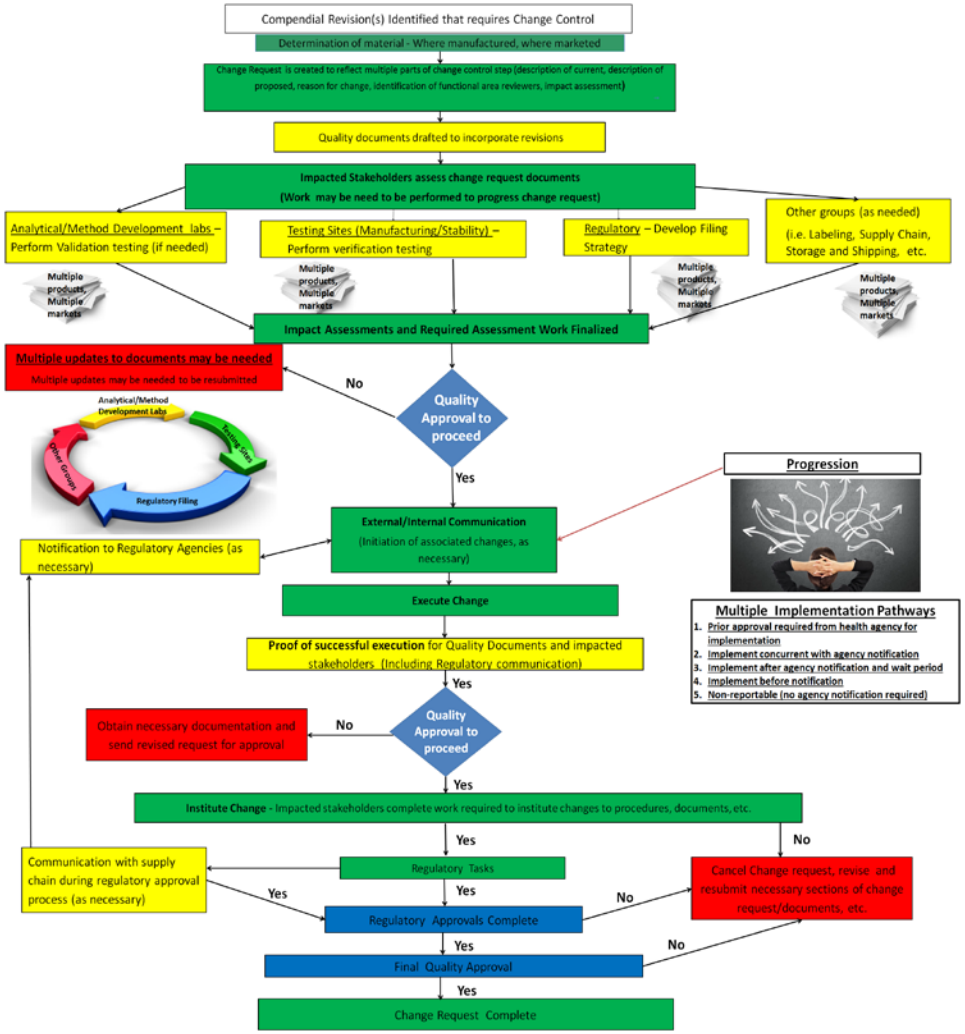
Change Control Impact Implementation Planning

- 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 . <661.1> and <661.2> &<661.3> proposed

2013

2015

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

Plan A
Plan B
Plan C

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

2016

FAQ Document
FAQ documented posted for clarification

2016

Plan A
Plan B
Plan C

PF 42.3
<661.3> introduced .

2016

PF 42.4
Additional revisions to <661.1> & <661.2>

2016

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

2017

Plan A
Plan B
Plan C

2017

PF 43.3
<661.3> replaced by <665> (expanded scope) .
<1665> replaced <1661.3>.

USP 41
Additional revisions to the chapter will be posted

2018

Plan A
Plan B
Plan C

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*

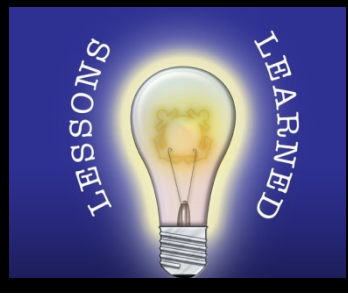
- Standard as written is understood by Expert Committee and Subject Matter Experts (SMEs) not necessarily the average user
  - Risk-based approach language is not clearly stated/understood
  - Risk-based approach assumes legacy products have data to meet <661>
- Scope – clarification needed
  - Chapter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

Difficulties Experienced by Industry
Cross referencing chapters

- 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

<381>
<660>/<1660>
<665>/<1665>

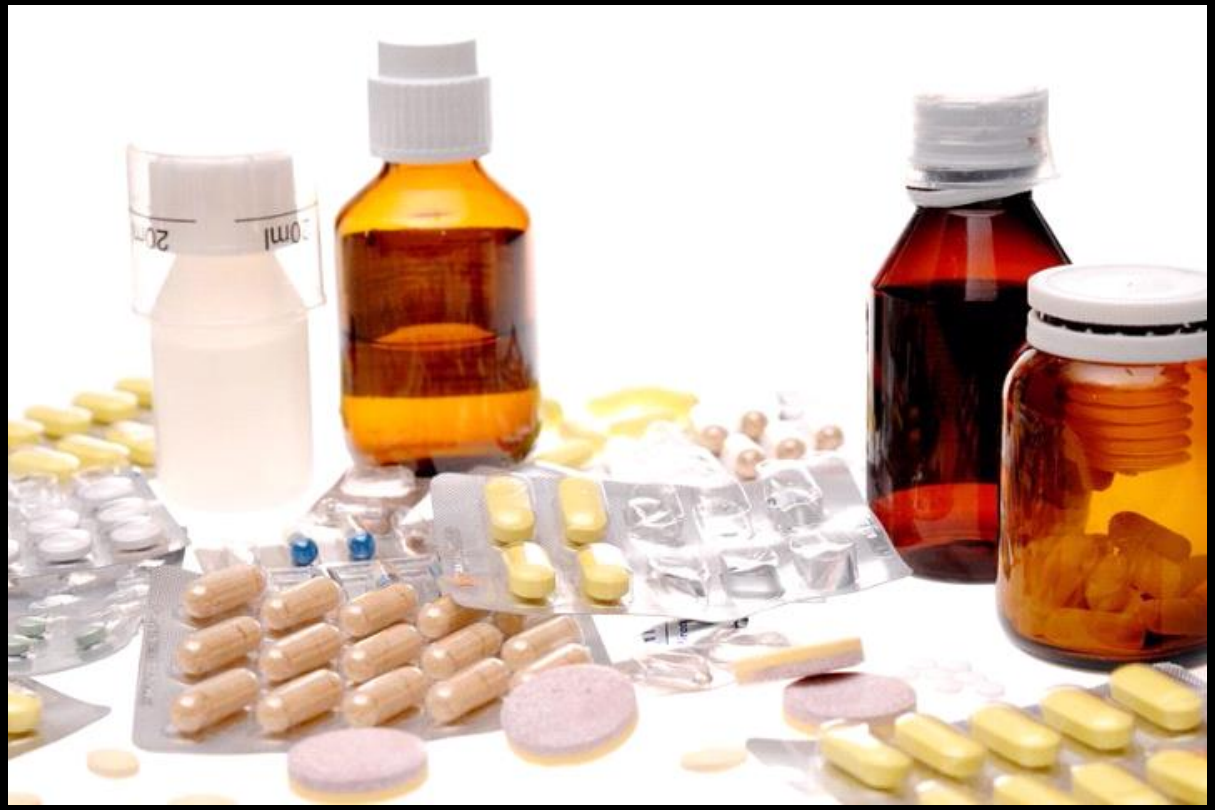
<381>

<381> ELASTOMERIC CLOSURES USED IN INJECTABLE PHARMACEUTICAL PACKAGING/ DELIVERY SYSTEMS

Industry Recommendations <381>

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



<660>, <1660>

<660> CONTAINERS—GLASS

<1660> EVALUATION OF THE INNER SURFACE DURABILITY OF GLASS CONTAINERS

Industry Recommendations <660>, <1660>

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

<665>, <1665>

<665> POLYMERIC COMPONENTS AND SYSTEMS USED IN THE MANUFACTURING OF PHARMACEUTICAL AND BIOPHARMACEUTICAL DRUG PRODUCTS

<1665> PLASTIC COMPONENTS AND SYSTEMS USED TO MANUFACTURE PHARMACEUTICAL DRUG PRODUCTS

Industry Recommendations <665>, <1665>

- 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

- Publish highly impactful revisions in PF
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- Develop feasible implementation timelines with Industry and FDA
- Develop future general chapter standards utilizing…
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Thank you so much