SUPAC IR/MR Update

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April 2013
SUPAC IR/MR Update

• Why do it?
  – Oral solid dosage forms continue to be the most significant class of drug product submissions to FDA (brand and generic)
  – SUPAC CMC updates are typically multi-faceted
    • Current SUPAC guidelines don’t accommodate multiple changes easily and therefore approvals are slow
    • SUPAC changes to MR products are particularly cumbersome
SUPAC IR/MR
Historical Context

• What is PQRI?
  – An organization of organizations
    • AAPS, CHPA, FDA, Health Canada, IPEC, USP
    • Working relationships with other scientific organizations such as NIPTE
  – Dues are used for workshops and research projects to explore cutting-edge projects
    • Ideas and manpower for projects come from member organizations
PQRI
Structure & Accomplishments

• Biologics Technical Committee
  – Sequential Design Working Group (WG)
  – Dissolution WG
  – BCS Class III WG
    • Biowaivers
  – IVIVC Considerations
    • Workshop proceeding in preparation
PQRI
Structure & Accomplishments

• Development Technical Committee
  – Stability Shelf Life WG*
  – Container Closure WG (update underway)
  – Sulfonate Esters WG*
  – Leachables & Extractables WG*

* Report available on website
PQRI
Structure & Accomplishments

• Manufacturing Technical Committee
  – SUPAC TDS Whitepaper*
  – Nanoparticle WG
  – SUPAC IR/MR Whitepaper

* Report available on website
SUPAC IR/MR

• Update Goal:

Bring new development science and principles to bear so that regulatory relief can be sought for IR & MR products

– QbD, design space and statistical principles
– ICH controls of excipients, APIs and development processes
– PAT and real-time testing control of manufacturing processes
– IVIVC principles for assurance of BE
Approach

• Multi-disciplinary team assembled by PQRI’s Manufacturing Technical Committee
  – Thirty authors representing a broad array of pharmaceutical scientists from industry and FDA (3)
  – Present the science that has evolved since the original 1992 SUPAC IR/MR guidance
  – Suggest how that science can be used to justify SUPAC changes
    • Case examples used to underscore concepts
Approach (Continued)

• Assemble the science, concepts and examples in a Whitepaper
  – Publish the Whitepaper and use as a focal point for further discussion by Academia, Industry (brand and generic) and Regulatory (worldwide) experts

• Principles can be cited in CMC submissions by companies making SUPAC submissions
Structure of the SUPAC IR/MR Whitepaper

- History
- Discussion of Current Principles Affecting Development
  - ICH (Q8, Q9, Q10 & Q11) - US Focused
  - Rest of world [Canada (NOC), Europe, Japan]
  - Quality by Design Principles
    - QTPPs, TPPs, CPPs, CQAs
  - Statistical approaches to formulation and process variables
    - Univariant and multivariant designs
Structure of the SUPAC IR/MR Whitepaper

- Process Analytical Technology
  - Value in process control
  - Role in supporting SUPAC changes
- Improvements in control of API
- Critical excipients (functionality)
- IVIVC considerations
  - Value in development, scale-up and approval
  - Value in post approval changes (biowaivers)
Structure of the SUPAC IR/MR Whitepaper

• Improvements in the Control of Product Scale-Up and Validation
• Improvements in Finished Product Testing
  – Real-time testing and release
• Future Trends
  – Batch v. continuous processing
Examples
Example – Design Space
Example – Formulation Factors & CQAs

**Formulation Design**
- Material Parameters
- API Attributes
  - Particle Size
  - Particle Shape
  - Density
  - Cohesivity
  - Flowability
  - Compressibility

**Excipient Attributes**
- Excipient Functionality
- Excipient Grade
- Excipient Particle Size
- Excipient Surface Area
- Excipient Molecular Weight/Polymerization/Viscosity
- API-Excipient Compatibility
  - Physical Compatibility
  - Chemical Compatibility

**Pre-blending**
- Process Parameters
  - Sieving
    - Screen Size
  - Sieving
    - Roll Pressure/Torque

**Granulation & Milling**
- Process Parameters
  - Granulation
    - Roll Pressure/Torque
  - Roll Speed/Tip Speed
  - Milling
    - Crusher Speed/Rotor Speed
  - Screen Size

**Blending & Final Blending**
- Process Parameters
  - Blending
    - Blend Time
  - Sieving
    - Screen Size
  - Milling
    - Lube Time

**Compression**
- Process Parameters
  - Speed
  - Force

**Film-Coating**
- Process Parameters
  - Spray Rate
  - Exhaust Air Temp

**Quality Attributes**
- Pre-Blend Uniformity
- Granulation Particle Size Distribution
- Final Blend Uniformity
  - Appearance
  - Hardness
  - Weight
  - Disintegration
  - Moisture Content
  - Tablet Content Uniformity
  - Tablet Content Uniformity
  - Dissolution
  - Purity

**Potential Critical**
- Material Attributes
- IPC Quality Attributes
- Attributes of Finished Product
### Example – PAT Impact on SUPAC

<table>
<thead>
<tr>
<th>Change Control Element</th>
<th>Current SUPAC IR/MR</th>
<th>Proposed QbD Approach</th>
</tr>
</thead>
<tbody>
<tr>
<td>Change Control Management</td>
<td>Highly specific in guidance documents for most elements</td>
<td>Follow principles outlined in ICH Q10</td>
</tr>
<tr>
<td>Types of Changes</td>
<td>Independent of product sensitivities</td>
<td>Product specific - changes impacting design space and control strategy as outlined in ICH Q8 &amp; Q10</td>
</tr>
<tr>
<td>Filing Documentation</td>
<td>Based on level of change</td>
<td>No filing documentation if within design space</td>
</tr>
</tbody>
</table>
Example – PAT & QbD Justification for SUPAC Changes

• IR Batch Size
  – Current SUPAC: 10 x biobatch size; stability commitment
  – Proposed SUPAC: Any multiple so long as within approved blend design space

• MR Level 2 change in rate-controlling coating level
  – Current SUPAC: PAS
  – Proposed SUPAC: No filing requirement if within design space and controlled by PAT
Example – Impact of API CQAs on Product Quality

Continuous Improvement / Lifecycle Management

- QTPP
- CQAs
- Potential Impact to Safety and Quality?
  - Yes
  - Low Risk
  - Severity
    - Low
    - High
  - High Risk

- Non-Critical

Potential Impact to Safety and Quality?

- Low Risk
- High Risk

Criticality Assessment
Conclusions

• The Whitepaper authors have set a challenging goal
  – Will the Whitepaper be effective in influencing regulatory change?

• Data from prior SUPAC publications suggests that success is possible
  – Do not expect FDA to issue an updated guidance; therefore:
    » Companies need to make this happen by judicious use of the principles found in the paper – good science should always prevail
Conclusions

• There may be increased up-front costs (and time) in development
  – Increased use of statistical approaches to product and process design
  – Conduct of IVIVC studies
  – Cost for PAT equipment, installation and use
  – Changes to plant design?
  – Changes to personnel responsibilities?
  – Addition of new personnel and/or retraining of existing personnel?
Conclusions

- Can increases in up-front costs be offset by greater flexibility in SUPAC changes?
  - Industry will need to collect and hopefully publish data to encourage innovation
  - FDA should publish data showing changes to approval time and approval category (CBE v PAS) to encourage utilization
What is next for PQRI?

• Publication of Proceedings of IVIVC Workshop
  – More in-depth discussion of IVIVC considerations
  – International in scope

Look for it 3Q 2013
Thank You

Q&A
Reference Slides
SUPAC TDS Publications

http://www.pqri.org/publications/index.asp

Link to SUPAC TDS publication:
http://www.pqri.org/pdfs/PharmSciTech-article.pdf

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