LEVERAGING AN EFFECTIVE PQS FOR SUCCESSFUL IMPLEMENTATION OF ICH Q12

CASSS CMC STRATEGY FORUM
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INTRODUCTION

• ICH Q12 is a transformative document – provides global regulatory framework for management of post-approval CMC changes
  o Varying stages of implementation across both health authorities and industry
  o Challenges related to legal constraints in some regions
• Q12 is built on concepts outlined in ICH Q8 (R2), Q9, Q10 and Q11
  o PQS outlined in Q10 is critical for successful implementation of Q12 concepts in product lifecycle management
  o *PQS is critical in effective change management to support Q12 implementation*
• Recent FDA guidance
  o *Q12 Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management* – (final) replaces the prior established conditions guidance
  o *ICH Q12: Implementation Considerations for FDA-Regulated Products* – (draft) provides considerations in implementing Q12 concepts
AGENDA

• Pharmaceutical Quality System (PQS)
• Change control process
• Challenges
• Examples (leveraging an effective and robust PQS):
  o Effectiveness of a PQS in defining and managing ECs and non-ECs and regulatory reporting
    • Example 1: Changes to sterile filters
    • Example 2: Tech transfer to drug product manufacturing site
• Amgen’s approach to ICH Q12 and expected challenges
PHARMACEUTICAL QUALITY SYSTEM (PQS)

In Alignment with ICH Q10:

- Achieves main objectives and enhances GMP requirements
- Enables knowledge and quality risk management
- Consistently demonstrates product and process understanding to enable risk based post-approval change management
PHARMACEUTICAL QUALITY SYSTEM (PQS)

- Establish standards that translate quality and regulatory requirements into procedures
- Consistently applied to all operations and products to ensure quality and regulatory compliance
- Ensures that changes to manufacturing or testing of a product can be effectively managed to ensure no adverse impact to product quality
- Can appropriately identify and mitigate risk, develop robust plans for change implementation, and assess impact to product quality

- Consists of distinct quality processes necessary for ICH Q12 implementation, including:
  - Quality Risk Management
  - Stability
  - Process/Product Development and Design
  - Product Specifications and In-process Controls
  - Manufacturing
  - Validation
  - Contamination Control
  - Change Control
  - Supplier Management
A robust change control management system can effectively manage change and minimize risk to product quality.
EFFECTIVENESS OF A PQS

- **Challenges:** how do sponsors demonstrate effectiveness of PQS in filing and provide appropriate level of detail to justify ECs and proposed reporting categories? An effective PQS per ICH Q10 in compliance with regional GMPs are necessary
  - All changes are managed through the company’s PQS and leverage prior knowledge and change management principles
  - Subject to inspection

- **For changes that are no longer reported, what are the concerns/expectations from regulators?**
  - Complexities due to regional reporting requirements, harmonization is critical to achieving full potential of ICH Q12
  - *PQS fundamentally not changing in terms of how we assess and manage changes*
EXAMPLE 1: REDUCTION IN FILTER SIZE/INCREASE IN FILTRATION PRESSURE

<table>
<thead>
<tr>
<th>Change description (32P33 Description of Manufacturing Process and Process Controls)</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduction in filter size/increase in filtration pressure. Acceptable data during validation.</td>
<td>During filter validation, a change in the extractable/leachable profile observed within acceptable range between filter 1 and filter 2</td>
<td>Unacceptable extractable/leachable identified during validation, or detection of bioburden post-filtration (unacceptable validation data)</td>
<td>Filter validation data (sterility assurance)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Data package required per PQS</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Reported/Supporting Information</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Filter supplier. <strong>Rationale:</strong> Risk assessments and appropriate experimentation prior to implementation of change ensures minimal impact to product quality for standard, like-for-like filter change.</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Notification Low</th>
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<tbody>
<tr>
<td><strong>Rationale:</strong> Sterility assurance is assessed through filter validation and data is available on inspection. Impact to product quality can be assessed through routine lot-release and in-process testing. Monitor on long-term stability.</td>
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<table>
<thead>
<tr>
<th>Notification Moderate</th>
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<tbody>
<tr>
<td><strong>Rationale:</strong> Increase in reportability due to differences in extractable/leachable profile during validation. Poses potential risk to product quality and therefore requires communication and review by FDA.</td>
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<table>
<thead>
<tr>
<th>Prior Approval</th>
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</table>

<table>
<thead>
<tr>
<th>Not Filed (change not implemented)</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>Rationale: Unacceptable risk to product quality. Filter is not used in manufacturing and change is not filed.</td>
<td></td>
</tr>
</tbody>
</table>
## EXAMPLE 2: DRUG PRODUCT TECH TRANSFER

<table>
<thead>
<tr>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change description</strong></td>
<td>Tech transfer to internal-owned DP manufacturing facility</td>
<td>Tech transfer to a CMO DP manufacturing facility with quality agreement in place</td>
</tr>
<tr>
<td>(32P31 Manufacturer(s))</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Data package required per PQS | PPQ, aseptic process validation, sterilization validation, internal comparability protocols with established acceptance criteria for comparability |

### Not Reported/Supporting Information
- Development testing sites. **Rationale:** Labs are required to follow any GLP and GMP procedures; data reviewed by SMEs and management.
- Distribution sites. **Rationale:** Change in distribution site expected to have minimal impact to product quality

| Notification Low | - | - | - |
| Notification Moderate | **(Multi-site PACMP)** **Rationale:** Data meets acceptance criteria provided in pre-defined validation and comparability protocols. Data provided in submission. | **(Site-specific PACMP)** **Rationale:** Data meets acceptance criteria provided in pre-defined validation and comparability protocols. Data provided in submission. | - |

| Prior Approval | - | - | **Rationale:** Increase in reportability due to potential risk to product quality |
| Not Filed (change not implemented) | - | - | - |

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**Increasing potential risk to product quality**

All 3 scenarios leverage effective change management via the PQS designed to control risk to product quality.
APPROACH TO ICH Q12

• Regulatory strategy and messaging
  o Have a mature, effective PQS capable of supporting ICH Q12 concepts
  o Proposed ECs and reporting categories are based on understanding of process and product knowledge, commercial manufacture, and established effective change management
    • In general, expect most changes to be reported through the Annual Report or managed by the PQS
    • Pursue ICH Q12 concepts outside of external expectations to alleviate regulatory burden where scientifically justifiable

• Current state
  o Implementation of ICH Q12 principles are in initial phases of implementation
  o Internal ICH Q12 workstreams are developing tools to implement Q12 principles across functions
EXPECTED CHALLENGES

- **Aligning with team on proposed reporting category and corresponding justification**
  - Lack of clarity on the vision of ICH Q12 and Established Conditions and aligning proposed reporting categories to current expectations
  - Where to push beyond existing regulations based on experience and available supporting data
  - General uncertainties around the proposed approach and appropriate level of detail
  - For established, legacy products – how to explain and justify what is not chosen as ECs

- **Will require significant recourses**
  - Development and justifications needed to establish a Product Life Cycle Management Plan
  - Redundancy of Product Life Cycle Management Plan with Module 2 and Module 3 content
  - Training on ICH Q12 principles for both industry and regulators is needed (ICH Q12 training recently published)

- **Will be held to existing regulations, or will request beyond what we file historically (i.e. IPCs)**
- **Consistency of approach across different reviewers and divisions**
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THANK YOU!

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