FDA Perspectives on Established Conditions and ICH Q12

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Disclosure

• The views presented do not necessarily reflect the views of ICH.
The Rationale for ICH Q12

• Implementation of Q8-Q11 provides a science- and risk-based approach to postapproval change management
  – Q8-Q11 focus on product development

• Opportunities for flexibility in post-approval change management have not been fully realized
  – Different requirements around the world are a disincentive to making improvements to increase process robustness

• Lack of alignment exists regarding necessary information and level of detail in the regulatory dossier
  – So-called “regulatory commitments” impact on post-approval change management

ICH Q12 proposed by the Informal Quality Discussion Group (IQDG) and accepted by the ICH Steering Committee in Minneapolis, June 2014
Q12 EWG Participants

• Diversity of technical expertise (small and large molecule, development, manufacturing, quality and regulatory, assessors and inspectors)

• FDA, PhRMA, EU/EMA, EFPIA, MHLW/PMDA, JPMA, Swissmedic, Health Canada

• APIC, IGPA, BIO, WHO, WSMI, DoH Chinese Taipei, DRA Singapore, ANVISA, EAC
Objectives

• A harmonized approach on technical and regulatory considerations for lifecycle management
• Enable a maximally efficient, agile, flexible pharmaceutical manufacturing sector that reliably produces high-quality drug products without extensive regulatory oversight
• Many manufacturing changes are managed effectively under the company’s Pharmaceutical Quality System (PQS) without the need for regulatory approval prior to implementation
• Manufacturers are encouraged to consistently pursue continual improvement, leading to better assurance of supply and opportunities for innovation
• Realized for small and large molecule products, new and currently marketed products, innovator and generic
Potential Benefits to Q12

• Reduce unnecessary cost and time burdens on industry and regulators, while assuring that patients reliably have access to high quality therapies
  – Realize benefit from application of current and innovative manufacturing technologies on a timely basis
• Enable and encourage increased transparency
  – between industry and regulators
  – between MAH and (contract) manufacturers
  – between reviewers and inspectors
• Harmonization across ICH regions plus potential for application in non-ICH countries
How do we get there?

- Science- and risk-based approaches to assessment of changes across the product lifecycle
- Effective management of knowledge by manufacturer
- Enhanced transparency and trust between manufacturer and regulator
- Improved use of harmonized tools (new and existing)
  - Established conditions
  - Proactive product lifecycle management strategy
  - Application of Q12 approaches for currently marketed products
  - Postapproval change management protocols

Tell and do → Do and tell

PAS, CBE → AR, PQS only
Proposed for Inclusion in Q12

- Guiding principles
  - Risk-based categorization of postapproval CMC changes
- Established Conditions (ECs)
  - Defining ECs
  - Revision of ECs
  - Considerations for currently marketed products
- Postapproval change management protocols
- Product Lifecycle Management Strategy
- Pharmaceutical Quality System and Change Management
- Relationship Between Assessment and Inspection
- Postapproval Changes for Currently Marketed Products
Risk-based categorization of postapproval CMC changes

- Concept of establishing reporting requirements for postapproval changes commensurate with risk
- Provides flexibility in regulatory approach and facilitates use of PACMPs
- Potential for regulatory convergence across regions
Established Conditions (ECs)

- Established Conditions
  - CTD does not provide for harmonized understanding or approaches to defining which information in a dossier would require a post-approval regulatory action (e.g., submission of a supplement, variation) if changed post approval
  - Established conditions determined at time of initial approval; if changed, reporting required

- Revision of Established Conditions
  - Once elements of ECs defined, how monitored, updated (add, subtract, modify)

- Considerations for currently marketed products
  - MAH can request to establish detailed ECs through a postapproval submission
  - Consider postapproval changes in the context of high level ECs that can apply to all currently marketed products
Postapproval Change Management Protocols

• Also known as “Comparability Protocols”
• Regulatory tool for post-approval changes
  • Outline specific future change(s) to be made
  • Tests, studies, etc. to be conducted to verify acceptability of change
  • Propose reporting category; often reduced compared to existing guidance
• FDA issued revised draft guidance “Comparability Protocols - Chemistry, Manufacturing, and Controls” in April 2016
• EU introduced Post-approval change management protocols (PACMPs) in 2010
• Similar concepts in both FDA and EU approaches
• MHLW/PMDA has indicated intention to allow PACMPs; under consideration by Health Canada
PQS and CM

- Building on elements of Q10 and enabled by Quality Risk Management (QRM)
  - Effective change management
  - Corrective Action and Preventive Action (CAPA)
  - Process Performance and Product Quality Monitoring System (PPPQMS)
  - Management review
  - Outsourcing and the PQS
  - Benefits of an effective PQS
  - Use of knowledge management in lifecycle management
Application of Q12 to Currently Marketed Products

- How to apply Q12 tools for currently marketed products that do not have Established Conditions
  - A priority for Q12 EWG given number of products already marketed

- Considering several approaches:
  - Provide guidance for changes where technical requirements addressed in existing ICH guidelines
  - Use of broad PACMPs for certain changes across multiple products and/or multiple sites

- Still under discussion
More on Established Conditions

• Working definition of Established Conditions:
  – legally binding information defined in an approved Marketing Authorization Application (MAA)
  – any change to an established condition, as defined in an approved application, would initiate a post-approval regulatory submission (e.g., supplement, variation, partial change application, etc.).

• Principles to identify what information may be proposed as ECs:
  – an assessment of criticality and management of risk (as described in ICH Q8 and Q9) to determine which information may be critical process parameters (CPP) and critical quality attributes (CQA)
  – the development strategy
  – product characterization
  – the control strategy (control strategy as defined in ICH Q10)
  – the desired product performance
FDA Perspectives on ECs

• ECs should:
  • provide an opportunity for regulators to avoid trying to serve as the manufacturer’s quality assurance unit, but instead spend resources to
    • verify appropriate and well-functioning PQS is in place (per ICH Q10 and Q12)
    • focus review and inspection efforts on facilities, products, and operations that pose the highest risk to patients, where there is insufficient understanding demonstrated to adequately mitigate that risk
  • encourage monitoring and trending (i.e., continued process verification) to identify opportunities for improvement
FDA Perspectives on ECs

• FDA published draft guidance “Established Conditions: Reportable Changes for Approved Drug and Biologic Products” in 2015
  • Intent to publicly describe and request comment on FDA’s thinking regarding this topic and to support development of Q12
  • Describes which elements of the control strategy could be considered ECs
FDA Perspectives on ECs
Linking ECs to Control Strategy

**Supportive** of product, process, controls, etc.

**Overall** control strategy including facility, environmental controls, etc. (Not typically reported in submission)

Elements **necessary** to assure process performance and product quality.
FDA Perspectives on ECs
Linking ECs to Change Management

Foundation: All changes are managed under the PQS

Managed solely by PQS

Changes reportable Post-approval
FDA Perspectives – Potential Benefits of ECs

• Increase transparency
• Reduce submission of unnecessary supplements
  – Effective post approval submission strategies
• Encourage continual process improvements
• Allows FDA to better regulate post-approval changes
  – More flexibility/responsibility for manufacturer
  – Risk based principles allow better focus on most important information and changes
  – Clarity for investigators on inspection
FDA Perspectives – Pending Issues

• How will it work?
  – Proposed ECs submitted by the applicant – M2? M1? Other?
  – Evaluated by the Agency
  – How will “final set” of ECs be communicated for lifecycle review and for investigators?

• How does the regulator decide?
  – Selection of ECs informed by:
    • Complexity/ability to characterize risk
    • Development data/studies
    • Product and process understanding
    • Risk assessment and mitigation strategies
  – May require discussion with other parts of the review team – risks not addressed by certain elements of the control strategy may be addressed by others (i.e., redundancy)
FDA Perspectives – Potential Challenges

• Need to focus decision-making on identifying the critical elements to ensure product quality, not “which changes would a reviewer want to see”

• Not “one size fits all”

• Learning process
  – Will need training within each regulator (assessors, inspectors)
  – Desire for consistency (where possible) across regions as well
Next Steps for ICH Q12

Progress in Lisbon, June 2016

• Good progress and general agreement on chapter drafts for:
  • Established Conditions
  • Post Approval Change Management Protocols
  • Product Lifecycle Management Strategy
  • PQS Effectiveness and Change Management
  • Categorization of change and data requirements/stability

• Application of Q12 for Currently Marketed Products
  • Agreement on scientific principles and opportunities for innovation
  • Further discussion needed to identify an acceptable regulatory implementation pathway(s)

• EWG aims to reach Step 1 Technical Document in June 2017
Conclusions

• ICH Q12 provides opportunities to:
  – Bring the science- and risk-based concepts in Q8-11 to the postmarket phase of the lifecycle
  – Encourage improved product and process understanding – during development and after commercialization
  – Enhance transparency and trust between manufacturers and regulators
  – Encourage proactive lifecycle management and continuous improvement
  – Harmonize tools and approaches to lifecycle management within ICH regions and beyond

• Improving assurance of supply and patient access to quality medicines
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Thank you!