ICH Q12
Technical and Regulatory Considerations for Pharmaceutical Product Lifecycle Management

Keith O. Webber, Ph.D.
Sr. Director, Global Regulator Affairs – Rx
Perrigo Company, plc

Disclaimer

- This presentation reflects the speaker's perspective on this topic and does not necessarily represent the views of Perrigo Company.

Challenges for Generic Drug Development

Competition

- First-to-File (P-IV submissions)
  - 180-day marketing exclusivity
  - 30-month forfeiture date
  - 30-month stay of approval
- First-to-Market (P-I, II, & III submissions)

Challenges for Generic Drug Development

Demonstration of “sameness”

- Availability of the Reference Product
- API
  - Morphology
  - Impurities
  - Residual solvents
- Finished dosage form
  - Excipients
  - Impurities
  - Dissolution

Challenges for Generic Drug Development

Demonstration of Bioequivalence

- Confidence interval-based as opposed to clinical relevance-based

Q12 – Vision and Goals

- Promote innovation and continual improvement
- Improve regulators' understanding and confidence in manufacturers' Pharmaceutical Quality Systems for management of post-approval changes
- Facilitate risk-based regulatory oversight
- Harmonize change management

Major Components of ICH Q12

- Regulatory Commitments
  - aka - Established Conditions
  - aka – Approved Matters
- Post Approval Change Management Protocols
- Assurance of a Company's PQS

Regulatory Commitments
[Established Conditions (USA) or Approved Matters (JP)]

Def.: Certain binding information concerning the manufacture and control of a pharmaceutical product.

- Proposed by the applicant and approved by the regulatory authority
- Supplement, Variation, or Notification is required to change them post-approval
- May be classified according to the regulatory action proposed to allow such a post-approval change.

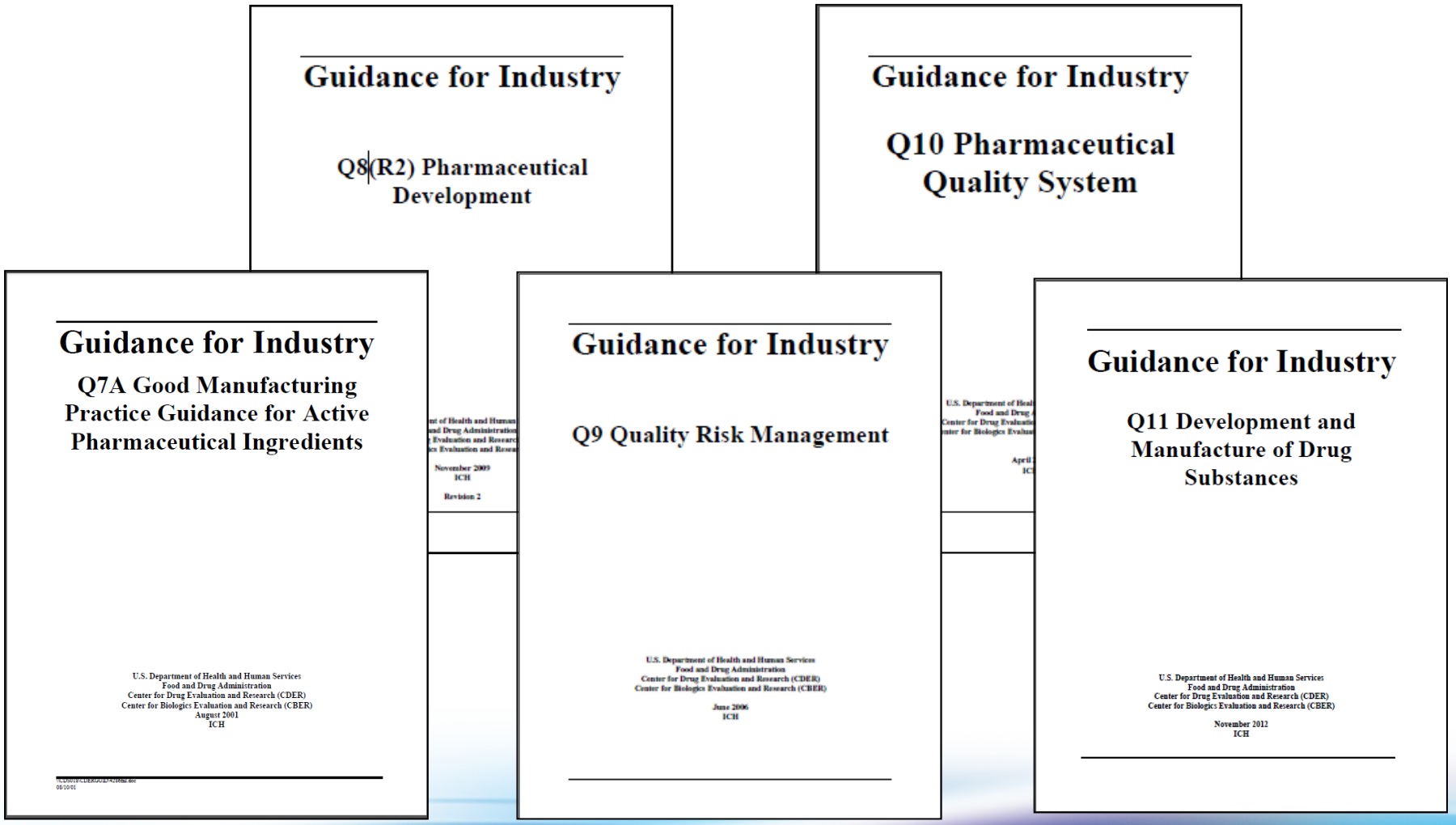
Post-Approval Change Management Protocol

- A regulatory tool that facilitates approval of CMC changes to an approved marketing application by enabling prospective planning of future change(s) including the assessment of the impact of the proposed change(s) on product quality.

Assurance of a Company's PQS

- Determined by inspection
- Based on compliance with ICH Q10

Q12 must be implemented in conjunction with other ICH guidance documents



Benefits & Risks of Q12 for the Generic Drug Industry

Benefits

- Increased focus on quality assurance
- Stimulation of innovation & continual improvement
- Streamlined post-approval change implementation
- Fewer prior-approval supplements

Increased focus on quality assurance

- Established Conditions = CQAs + CPPs
- Greater focus on factors that contribute to quality and performance

Stimulated innovation & continual improvement

Increased ability to make improvements to:

- Analytical methods
- Equipment
- Manufacturing methods
- Quality control methods

Streamlined post-approval change implementation

Do & Tell when:

- Established Conditions don't change
- A PACMP is implemented
- Company has an acceptable PQS

Benefits & Risks of Q12 for the Generic Drug Industry

Risks

- Longer review times?
- More questions from regulators?
- Increased number of review cycles?
- ECs increase in detail rather that decrease?
- Shift of supplements from CBE30 to PAS?

Post-Approval Change Management Protocols

A PACMP typically involves two steps:

- Submission of a protocol describing the proposed change, its rationale, risk assessment and proposed studies & acceptance criteria to assess the impact of the change(s);
  - The protocol is approved by the regulatory authorities in advance of the implementation of the proposed changes.
- Submission of the actual results/data based on the approved protocol.

Utility of a PACMP - Example

- Prepare PACMP
- Manufacture product using the change
- Submit PACMP for review
- FDA reviews while you collect stability data (~6 months)
- Upon approval of PACMP, submit final data (e.g., CBE-30)
- Launch at day 31

Blue Sky Potential for PACMPs

- A single PACMP for a group of changes for a single product
- A single PACMP for changes that would be implemented across multiple products (e.g., change in stopper across multiple products) and/or at multiple sites (change in analytical method across multiple sites)
- Utilization of PACMPs as a ‘one-step’ process

Changing API source under Q12 - Example

Established conditions	Changing?
Approved API source & site	Yes
Approved API specifications	No
Approved starting materials	No
Approved API manufacturing process (?)	No

Changing API source under Q12 - Example

PACMP Protocol Steps
Verify cGMP compliance of new site (FDA Inspection & Audit)
Test two lots of API and ensure they meet specs
Manufacture finished dosage form and ensure that it meets specs.
Place samples on stability to demonstrate compliance with stability specs.
Go to Market

IGPA Representatives on Q12 EWG

- Keith Webber – Perrigo Co.
- Nick Cappuccino – Dr. Reddy's Labs
- Graham Powell – Mylan (UK)
- Takeshi Sugiura – Towa Pharma (Japan)

In Closing

- ICH Q12 has great potential to support innovation and continual improvement in the post-approval period.
- The EWG is working cooperatively across the industry and regulatory components to achieve these goals.
- Visionary implementation of the final guideline will be critical to its success.