ICH Q12: Challenges, Opportunities …
and more Challenges

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Presentation Outline

N.B. Views presented are personal and do not necessarily represent those of Health Canada or the ICH …… yet. 😊

• **Why develop ICH Q12?**

• Harmonization aspirations and challenges
  – Reporting categories
  – Established Conditions
  – Post-Approval Changes Management Protocols
  – “Downstream Effects”
From ICH Q12 Concept Paper (1)

• Action proposed
  – will promote innovation and continual improvement, and strengthen quality assurance and reliable supply of product, including proactive planning of supply chain adjustments
  – will allow regulators (assessors and inspectors) to better understand, and have more confidence and trust in a firm’s pharmaceutical quality system (PQS) for management of post-approval CMC changes

• Perceived problems
  – lack of a harmonized approach on technical and regulatory considerations for lifecycle management
  – gaps exist which limit full realization of intended benefits of Q8-11 and the envisioned post-approval ‘operational flexibility’ has not been achieved
  – inconsistent utilization of PACM Plans and Protocols - so opportunities to strategically and prospectively manage anticipated changes (despite enhanced product knowledge and process understanding) have not been fully realized
From ICH Q12 Concept Paper (2)

• Issues to be Resolved

  – Regulatory Dossier
    • Explore development of harmonized approach to “regulatory commitments”
    • Delineate the information & associated detail needed in the dossier for regulatory assessment and inspection, thereby enabling post-approval change

  – PQS
    • Establish criteria for a harmonized risk-based change management system based on product, process and/or clinical knowledge that effectively evaluates the impact of change on quality and, as applicable, to safety and efficacy
    • Clarify expectations & convey the need to maintain a knowledge management system that ensures continuity of product & process information over the product lifecycle
From ICH Q12 Concept Paper (3)

- Issues to be Resolved (cont.)

  - Post Approval Change Management Plans and Protocols

    - Introduce the concept of a PACM Plan that can be used: to proactively identify post-approval changes and the mechanisms for submission; and, for assessment by regulatory authorities (Assessors and Inspectors)

    - Establish criteria for PACM protocols that can be adopted by the ICH regions (enabling a harmonized proactive approach for lifecycle management)

    - Encourage enhanced product development and control strategy approaches (QbD) providing opportunities for scientific and risk-based foundations for PACM Plans
Great – let’s get started!

• Too difficult to harmonize all the details around manufacturing changes and suitable reporting requirements, especially considering differing regulations (…. and they’re considered too demanding and inflexible anyway) …. 

So …..
• Capture concept of regulatory relief based on reducing number of Established Conditions, and/or removing or downgrading reporting requirements based on knowledge, experience, and established trust.
• Harmonize aspects of Post-Approval Change Management Protocols and expand the number of ICH members allowing their use
• Increase communication between evaluators and inspectors

And ….. Job done!
Not so fast!

- Will new “transformational” approaches be broadly accepted & used?
- Can Q12 establish new paradigms and provide “regulatory relief” that Design Spaces couldn’t?
- It seems that concerns about non-critical parameters, extensive data requirements, time & costs of development may have all contributed to the limited creation and/or acceptance of Design Spaces.

BUT

- What indicators are there that the regulators involved, or the associated concerns, have changed? Or that existing regulations can be side-stepped without a new formal mechanism? (Will we have a mechanism”?)
- It’s hard to imagine that if the already industry-regulator-harmonized design space paradigm didn’t work, that something “softer” (less well defined?), based on “confidence” in the MAH’s product experience, knowledge management and quality system, will be accepted as grounds for extensive regulatory relief.

There is a lot of work to do!
Presentation Outline

• Why develop ICH Q12?

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  – “Downstream Effects”
Categorization of manufacturing changes requiring communication with the regulator (1)

- Categorization exists in all current ICH member regulatory jurisdictions with varying reliance on regulations versus guidance
- Categories rationalized according to risk to patient (or product/process)
- Systems not harmonized re. number of categories, data expectations, timeframes for review
- All jurisdictions include at least one category requiring prior-approval and at least one category requiring notification
- Flexibility can be captured by indicating that if certain “conditions” are met regarding a change, the reporting requirement drops (or, conversely, if not met the reporting requirement moves up)
Categorization of manufacturing changes requiring communication with the regulator (2)

• The use of formal submission/reporting categories is currently, and will continue to be, the “workhorse” approach to accomplish manufacturing changes in ICH-member, and ICH-observant, regulatory jurisdictions, and is not described in current ICH guidance.

• It is an enabler (perhaps essential) for the adoption (best use?) of Post-Approval Change Management Protocols.

• Exemplification in Q12 will make the guideline more relevant to a broader group of regulatory jurisdictions; and may help encourage broader use, and high-level harmonisation, of risk-based reporting categories in those jurisdictions.

• It provides for high-level “connection” with new WHO guidance, e.g, “Guidelines for procedures and data requirements for changes to approved vaccines” (and a biotherapeutics guideline under development).
Established Conditions and the potential for leveraging “regulatory relief” (1)

- EC essentially means “communicate the change”
- EC becomes associated with a reporting category
  - Pre-approval (upper, lower), Notification, Annual Report
  - In Japan only one “Pre”, one Notification & and no submitted Annual Report
- Do already marketed products have ECs?
  - Negotiated EC versus Default EC (captured in regulation/guidance)

- For analytical methods, some ECs could (perhaps) be method outcomes rather than method parameters
- Other “outcome-based” approaches may be possible for manufacturing process unit operations

BUT
- Can a significant change captured in existing regulation and guidance really be negotiated to be “off the radar”?
Established Conditions and the potential for leveraging “regulatory relief” (2)

- Link “negotiated” EC to “negotiated” reporting category during submission review?
- Based on what?
  - “High-functioning” PQS, + knowledge, + experience, + “je ne sais quoi”? 
- Need “score card” for consistency (inter-agency, -division, -review team)
  - But inter-agency harmonization presents major challenge 
- How is “agreement” captured? (for sharing with inspectors, other agencies) 
- Even using a score card, if “agreement” can be specific to MAH, product, manufacturing site - and be different between regulatory jurisdictions, disharmony will increase
Established Conditions and the potential for leveraging “regulatory relief” (3)

- Existing regulation/guidance would have to defer to the negotiated reporting category
- Regulatory screening of submission for correct reporting category gets very complicated!
- Identifying (and correcting) reporting errors may present a problem if notifications are not formally screened

BUT

- How about implementation via “multi-element” PACM Protocols?
  - Based on a currently acceptable regulatory mechanism (now expanding)
  - Details are captured and assessable
  - Could be shared with, and possibly accepted by, other jurisdictions
A possible new life for PACM Protocols

- Currently under-used wherever use is possible
- Concept/use to become adopted by remaining ICH members via ICH Q12
- Chance to harmonize approach amongst ICH members (to extent possible)
- Multi-element PACM Protocols could give “more bang for the buck”
  - Same change across multiple products?
  - Same change across multiple sites?
- MAH can choose not to use the PACMP, without penalty
Potential for longer-term downstream effects within and beyond current ICH jurisdictions

• “ICH-ing” ECs, reporting categories & PACMPs will encourage broader adoption

• Possibility for ICH-independent harmonization and regulatory convergence

• Possible “benchmark-agency”-based acceptance of 1st step of PACMPs with national/sovereign/accountable decision at 2nd step?
Some additional points under consideration

- For some approaches being considered in Q12, issues exist relating to the difference in complexity of product/process for biologics relative to chemicals. Need to acknowledge and address where appropriate.

- Products in “regulator-granted” rapid development programs will be lacking in manufacturing experience, extent of product knowledge, batch numbers, etc., that would contribute to the “confidence” a regulator would need for the new MAH to realize some “benefits” intended to be possible through Q12. We should acknowledge these challenges. Focus of Q12 should not be only on the initial application.
Current focus of drafting groups

- Established Conditions
- Existing Products & Frequent Changes
- Life-Cycle Management Plans
- Post-Approval Change Management Protocols
- PQS & Assessor/Inspection interactions

Currently anticipated timeframe & milestones

- June 2016: face-to-face meeting to continue progress
- Meetings via teleconference
- November 2016: face-to-face meeting to continue progress. Generate version for extensive evaluation by EWG member “constituencies”.
- Meetings via teleconference
- June 2017: Step-1 Document (Step-2 via ICH Assembly approval) then release for public comment
- Meetings via teleconference: public comments received & addressed
- November 2017: Finalize Step-4 Document
Acknowledgements

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