Technical Change Management and the Need for Global Convergence

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“The man who moves a mountain begins by carrying away small stones.” - Confucius
Presentation Outline

- Challenges of global technical change management
- Essential elements for harmonized regulatory guidance
- Global convergence for technical change guidance; ICH Q12 and WHO
Presentation Outline

Challenges of global technical change management

Essential elements for harmonized regulatory guidance

Global convergence for technical change guidance; ICH Q12 and WHO
Factors that contribute to the challenges of technical change management

- Activity in up to ~140 countries
- Country specific registrations
- Global Supply Chain
- Multiple Sites Operating Globally

Country Specific Dossier
- ICH and non-ICH
- Declarations
- Details
- GMP documents

Reportable vs. non-reportable
- Data req’ts

Lack of consistent change categorization

Review and Approval Times
- HA Backlog
- Sequential submissions
- CPP Needed

The complexity that results from managing technical changes globally can result in drug shortages and hinders innovation
Case Study 1
A “minor” change to a test method

• Change description
  – In-Process Test
  – Modification of the test method for detecting potential viral contaminants
  – Identified as a critical step/test
Case Study 1:
Product A is registered in 127 countries at the time of the minor change
Case Study 1:
The submission was dispatched to all concerned countries in May-2011
Case Study 1:
Actual submission occurred following dispatch between May and December 2011

- **Within 30 days**
- **Submission not required**
- **Not submitted**
- **Within 6 months**
Case Study 1: The last approval took 20 months from submission and closure was after 26 months.
Case study 2: Change in Manufacturing Site

• Change description
  – Drug Product
  – Manufacturing Site Change
  – Technology Transfer
Case study 2
Product 2 is registered in 120 countries at the time of the Drug Product Site change
Case study 2:
The change was dispatched to all but three countries in 2 waves

Mar-Jun 2006

May – Jul 2007

Not required
Case study 2: The actual submission was performed within 10 months by the majority of countries.
Case study 2: The time from submission to approval – where recorded – varied substantially

- Not recorded
- 2-12 m
- Less than 1 m
- Not required
- More than 12 m
Case study 2: A majority of countries approved in 24 months after dispatch but global implementation took 41 months.
Presentation Outline

Challenges of global technical change management

Essential elements for harmonized regulatory guidance

Global convergence for technical change guidance; ICH Q12 and WHO
Essential elements for harmonized global post approval technical change management

- Consistent change classification and reporting
- Aligned data and content requirements (stability)
- Harmonized review and approval timelines (<6m)
- Risk-based approach for how to manage the change

The ultimate goal is to reduce or eliminate reporting of minor/low risk changes and to have a unified way of managing reportable changes.
## Comparison of Regional Change Guidances

<table>
<thead>
<tr>
<th>Risk</th>
<th>Approach/Region</th>
<th>EU</th>
<th>WHO (chemicals/vaccines)</th>
<th>GCC</th>
<th>ASEAN (chemicals)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Higher</td>
<td>«PRIOR APPROVAL »</td>
<td>Type II Variation</td>
<td>Major Variation Vmaj</td>
<td>Type II Variation</td>
<td>Type II Major Variation MaV</td>
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<tr>
<td>Moderate</td>
<td>«TELL, WAIT &amp; DO»</td>
<td>Type IB Variation</td>
<td>Minor Variation Vmin</td>
<td>Type IB Variation</td>
<td>Type I - Minor Variation-Prior Approval MiV-PA</td>
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<tr>
<td>Lower</td>
<td>«TELL &amp; DO»</td>
<td>Type IA_{IN} Variation</td>
<td>Immediate Notification IN</td>
<td>Type IA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>«DO &amp; TELL»</td>
<td>Type IA Variation</td>
<td>Annual Notification AN</td>
<td></td>
<td>Type I - Minor variation-Notification MiV-N</td>
</tr>
</tbody>
</table>
Presentation Outline

Challenges of global technical change management

Essential elements for harmonized regulatory guidance

Global convergence for technical change guidance; ICH Q12 and WHO
ICH PRESS RELEASE  
Lisbon, Portugal, 11-16 June 2016

ICH increases its global reach, moves forward on global drug development

The International Council for Harmonisation (ICH) met in Lisbon, Portugal, 11-16 June 2016, bringing together regulators and industry from around the world. Building on the objective to establish itself as a truly global platform for harmonisation for better health, ICH formally welcomed 2 new Members and 14 Observers representing regulatory authorities, regional health initiatives and pharmaceutical industry.

In addition to the 5 regulatory authorities and regional health initiatives announced in December 2015, ICH welcomed the following as new Observers:

- Association of Southeast Asian Nations (ASEAN)
- Biotechnology Innovation Organisation (BIO)
- Central Drugs Standard Control Organization (CDSCO, India)
- Council for International Organizations of Medical Sciences (CIOMS)
- Comisión Federal para la Protección contra Riesgos Sanitarios (COFEPRIS, Mexico)
- East African Community (EAC)
- European Directorate for the Quality of Medicines & HealthCare (EDQM)
- Health Sciences Authority (HSA, Singapore)
- International Pharmaceutical Excipient Council (IPEC)
- Ministry of Food and Drug Safety (MFDS, South Korea)
- Roszdravnadzor (Russia)
- Food and Drug Administration (TFDA, Chinese Taipei)
- Therapeutic Goods Administration (TGA, Australia)
- United States Pharmacopeia (USP)

Moreover, two new pharmaceutical industry bodies were welcomed, with International Generics and Biosimilars Association (IGBA) and World Self-Medication Industry (WSMI) accepted as Members.

Objective of ICH is to establish itself as a global platform for harmonization
ICH Q12 will help manage the complexity of change, but more is needed for transformational change

- Clarifying **established conditions** for manufacture and control based on risk, product type, development approaches, manufacturing experience, GMP status

- Development of **product lifecycle strategy**

- Provide **harmonized tools** to facilitate prospective changes over the product lifecycle, e.g. **change management protocols**

- Establish ICH **expectations** of assessment and implementation of frequent manufacturing changes
Can Established Conditions be globally accepted?

Benefits:

- EC’s will be based on process and product understanding; **non-EC’s are not reportable**
- Legally binding and subject to reporting
- Risk-based assessment defines the extent of data and reporting category

Challenges (ICH vs. non-ICH):

- Global implementation time (>5 years)
- May result in increased reporting and request for more details (increase in requirements)
- Country specific EC’s may not be avoidable
- Management of changing EC’s

Established Conditions based on “performance or output” will deliver what is needed for Q12 to be most effective
Can lifecycle management strategies, including protocols and monitoring plans provide expedient ways of managing change globally?

Benefits:

- Data availability (flexibility offered)
- Use of protocols/risk management plan with reduced reporting or no reporting
- Plan may help with frontloading of potential changes and how they will be managed

Challenges:

- Different regulatory legal framework
- Review timelines will not change – perhaps fewer submissions?
- Lack of harmonized data requirements
- Timing for adoption of Q12?
Driving global regulatory convergence

Efforts underway to develop a guideline for biotherapeutics leveraging the work for vaccines

World Health Organization

Guidelines for Procedures and Data Requirements for Changes to Approved Vaccines

NOTE:

This document has been prepared for the purpose of inviting comments and suggestions on the proposals contained therein, which will then be considered by the Expert Committee on Biological Standardization (ECBS). Publication of this early draft is to provide information about the Guidelines for Procedures and Data Requirements for Changes to Approved Vaccines to a broad audience and to improve transparency of the consultation process.

These Guidelines were developed based on the outcomes and consensus of the WHO consultation convened in 2013 with participants from national regulatory authorities, national control laboratories, vaccine manufacturers and academia researchers.

The text in its present form does not necessarily represent an agreed formulation of the Expert Committee on Biological Standardization. Written comments proposing modifications to this text MUST be received by 31 March 2014 in the Comment Form.
Concluding Thoughts

• Ultimate goal is to reduce and/or eliminate reporting of low risk changes and to have a unified way of managing reportable changes to enable us to maintain drug supply, compliance, and foster innovation

• ICH Q12 will provide what is needed to baseline reportable changes and to enable LCM, but more is needed.....

• Time is against us and we must find a way to align and progress on these very important initiatives
Global convergence of post-approval change regulations: a «Win-Win» outcome for all

<table>
<thead>
<tr>
<th>Harmonized post-approval regulations</th>
<th>Change classification, procedures, dossier requirements</th>
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<tbody>
<tr>
<td>Regulators</td>
<td>Industry</td>
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<tr>
<td>Prioritize based on criticality of change</td>
<td>Allow better planning / execution of changes</td>
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<tr>
<td>Facilitate assessment of changes</td>
<td>Enable more efficient use of resources</td>
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<tr>
<td>Enhance collaboration/ knowledge sharing with other agencies (ICH and non-ICH)</td>
<td>Reduce risk of non-compliance</td>
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<td>Reduce complexity in supply chain</td>
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Continuous and reliable supply of high quality drugs to all patients GLOBALLY

Mutual recognition of regulatory decisions

Transparency
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Vision for Global Convergence

One World

One Regulatory Standard