CMC Changes to Biotechnology Products: A Global Perspective from Industry

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All Changes are Not Considered Equal

Innovator Process Change
Governed by comparability guidance (ICH Q5E)

Nature of Process Change

<table>
<thead>
<tr>
<th>Change filter supplier</th>
<th>Move equipment within same facility</th>
<th>Move to new production facility (same company)</th>
<th>Change cell culture media</th>
<th>New cell line or major formulation change</th>
</tr>
</thead>
</table>

Risk Factor & Data Requirements

Lower Risk
Commonly implemented
- Analytical data
- Process studies

Moderate Risk
- Analytical data
- Process studies
- Stability data

Higher Risk
Less commonly implemented
- Analytical data
- Process studies
- Stability data
- Clinical data

Fundamental Basis of Comparability Guidance (Q5E)

Same Manufacturer, Same Product ..... 
Continuity of data, experience and knowledge about the product & process eg.
- Access to retention samples
- Ability to compare in-process parameters and samples
- Access to the drug substance
- Historical, data-based, understanding of critical quality and clinical attributes
Why Does a Firm Make Manufacturing or Analytical Changes?

- Clinical to commercial process and facility and scale
- New manufacturing technology
  - Media treatment technology to prevent Drug Substance Contamination
  - Isolator filling technology to prevent drug product contamination
- New testing methodology
  - Nuclear magnetic resonance (NMR) testing to detect raw material adulteration
  - Mass Spectrometry multi-attribute testing
- Regulatory agency requirements
  - Serialization of final product
- Learning more about your product and process
  - Variability of raw materials and process
- Prevention of Drug Shortages
  - Second sourcing of critical components and raw materials
  - Second facility for risk mitigation
Changes are introduced throughout product development and commercialization.

**Changes at Different Stages:**

- **Pre-Clinical Phase:**
  - Toxicity Studies
  - Process Development

- **Clinical Phases:**
  - Phase 1
  - Phase 2
  - Phase 3

- **Manufacturing Phases:**
  - Clinical Manufacturing
  - Commercial Manufacturing

- **Post Approval Phase:**
  - Typical Changes include:
    - Scale-up Bulk Process Formulation
    - Scale-up Drug Product Process Manufacturing Site
    - Post Approval Commercial Process (GMP)

- **Additional Changes:**
  - Clinical to Pivotal
  - Toxicology to FIH
  - Pivotal to Commercial

- **Key Milestones:**
  - Pre-Filing Mtg.
  - MA Filing
  - MA Approval
  - Commercial Sale

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*CMC Strategy Forum - Japan - 2013*
## cGMP Regulations and Quality Systems Require a Change Control Process and System

<table>
<thead>
<tr>
<th>Reporting Strategy Code</th>
<th>RA Assessment in System</th>
<th>Product May Be Distributed...</th>
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<tbody>
<tr>
<td><strong>A</strong> = Major Change; submit supplement/Variation and wait for approval</td>
<td>Reportable Approval required before distribution; Product Restriction = <strong>Yes</strong></td>
<td>after approval</td>
</tr>
<tr>
<td><strong>B</strong> = Major Change; submit notification; no approval required</td>
<td>Reportable Submit before distribution; Product Restriction = <strong>Yes</strong></td>
<td>after submission or after defined silence period (varies from country to country)</td>
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<tr>
<td><strong>C</strong> = Minor Change; submit on annual basis, or with major changes in a Type I Variation, Minor Change Notification</td>
<td>Reportable May distribute before submission; Product Restriction = <strong>No</strong></td>
<td>before submission, as change is implemented</td>
</tr>
<tr>
<td><strong>Y</strong> = Minor Change; submit on periodic interval or at time of product renewal</td>
<td>Reportable May distribute before submission; Product Restriction = <strong>No</strong></td>
<td>before submission, as change is implemented</td>
</tr>
<tr>
<td><strong>D</strong> = No Impact on registration; no filing required</td>
<td>Not Reportable Product Restriction = <strong>No</strong></td>
<td>as change is implemented</td>
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Problem Statement

- The number of CMC variations jeopardizes a firm’s ability to continuously supply patients, strains health authority resources and has the potential to negatively impact cost.

Supply planning is difficult for products with multiple number of unapproved variations

Health authorities are unable to keep up with current review demand – delay in approvals

Increasing inventory levels eases supply planning but with higher costs and scrap risk
Bringing a Global Change through Approval is often a multiple year endeavor even for the simplest of changes

**Core File Prep 2 m**

**EM File Prep 1-2 m**

**Core review cycle 4-10 m**

**Non-ref EM reviews 6 -20m**

**Ref EM reviews 6 -24m**

**Wave 1 (core) 6-12 month approval cycle (post data)**

**Wave 2 (non-ref countries) approval cycle 9-24 m**

**Wave 3 (ref-countries) approval cycle 12- 36 months (post data)**
Model Metrics for a single product with 4 new Prior Approval Supplements per year

- Wave 1 Countries (5 Jurisdictions)
  - Max Cycle time = 1 year
  - Potential of 4 versions per jurisdiction (CMC only)
  - 10 - 20 different supply strategies/restrictions per SKU

- Wave 2 Countries (up to 50 Jurisdictions)
  - Max Cycle time = 2 year
  - Potential of 8 versions per jurisdiction (CMC only)
  - 200 - 400 different supply strategies/restrictions per SKU

- Wave 3 countries (18 Jurisdictions)
  - Max Cycle time = 3 years
  - Potential of 12 versions per jurisdiction (CMC only)
  - 108 – 216 different supply strategies/restrictions per SKU

Requires 318 – 636 supply strategies/restrictions per product per SKU
Case Study: Additional Manufacturing Site for Drug Substance to 96 countries – 2009/2010
Key Challenges

• Change classification is different in various countries
  • minor change (notification only) to new registration

• Approval Timelines

• CPP* requirement in some countries
  • Country of Origin vs first approval

• Drug Substance stability requirement in some countries of 12 mos at time of filing

• Drug Product Stability requirement in some countries of 12 mos at time of filing

• Different country specific requirements
  • internal raw data (executed batch records)
  • Analytical raw data (chromatograms, spectrograms etc.), Certificates of Analysis
  • Declarations

*CPP = Certificate of Pharmaceutical Product
Approval timelines in major markets

Brazil
Taiwan
Thailand
Japan
South Africa
Mexico
Serbia
Israel
Turkey
Canada
Croatia
witzerland
Singapore
Australia
NeuZealand
EU
2009
2010
2011
2012
2013

12 months stability data for drug product

Dispatch to affiliates 1.Wave
Submission to MoH
Approval
Global Approval eventually received after 5 years

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**Nigeria, Palaestina.**
**Tajikistan, Saudi Arabia, Yemen**

**Jordan, Kazakstan, Oman, Tunisia**

**Guatemala, India, Kuwait, Kirgistan, Laos, Macedonia, Nepal, Senegal, Ukraine**

**Panama**

**Lybia, Russia, Sri Lanka, Tanzania, Venezuela**

**Ecuador, El Salvador, Georgia, Ghana, Honduras, Hong Kong, Jamaica, Kenya, Mauritius, Moldava, Myanmar, Nicaragua, Paraguay, Quatar, Saudi Arabia, Trinidad & Tobago, Turkmenistan, Uruguay, Uzbekistan, Vietnam**

**Lebanon, Philippines**

**Dispatch to all other countries in LATAM, APAC, Middle East, Eastern Europe, Africa**
Key Messages

• Adding a manufacturing site for a biotech DS can take up to **5 years** until global approval.

• Highly dynamic regulatory environment in some countries leads to **sometimes unpredictable/new country requirements beyond EU/US ICH standards** resulting in a lengthy Q&A process during Health authority review.

• Positive trends: most countries now allow multiple API sites
Harmonization across countries to facilitate worldwide drug availability?

- Pre approved change management plans reduce the review and approval time
  - US – Comparability Protocols
  - EU – Post Approval Change Management Protocol (PACMP)

- For CPP countries, recognition of change approval from reference agency?

- Harmonization opportunities through WHO, ICH, ASEAN, APEC or other unifying bodies
  - Risk based variation requirements
  - Alignment of reporting categories

- “tell, wait, and do” in cases of safety and quality risks
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