Risk-Based Change Management Using QbD Principles

Lynne Krummen, Ph.D.
VP, Global Head, Technical Regulatory Biologics
Genentech, a member of the Roche Group

CMC Forum 2013
Tokyo, Japan
Presentation Outline

• Management of Post-Approval Change Using Risk-Based Comparability Concepts
  • What, Why and How
  • Key Scientific Principles

• Risk-based Lifecycle Management and Regulatory Strategies
  • Expanded Change (Comparability Protocols)
  • Lifecycle Management
Post-approval CMC Changes

• Post-approval comparability exercises are often associated with the following changes:
  
• Maintenance of Supply
  – Site transfer/addition including scale-up
  – Process improvements to increase product titer to meet forecasted demand

• Process Improvements
  – New manufacturing technology
    • Media treatment technology to prevent Drug Substance Contamination
    • Isolator filling technology to prevent drug product contamination
  – Improved controls
    • Improvements in microbiological controls
    • New methods to detect raw material adulteration
  – Improved testing methodology
    • Mass Spectrometry multi-attribute testing
Problem Statement:

- Low-risk, post-approval CMC changes that are reportable and require pre-approval are quite common.
- These changes can often be quite well understood.
- Different global post-approval CMC filing requirements and long approval timelines are not proportional to risk.
  - Jeopardize a firm’s ability to continuously supply patients.
  - Creates compliance gaps.
  - Strains both industry and health authority resources.
  - Increases cost, quality and supply risk.

One World

One Product
Comparability: ICH Definitions:

**What:** Comparability is the demonstration of a high degree of similarity between products produced by different manufacturing processes, equipment and/or sites, such that no adverse impact on quality, safety or efficacy occurs.

**Why:** Comparability is an essential activity required to support product lifecycle management and continual improvement, to facilitate regulatory approval and ensure consistent delivery of product to our customer.

- Demonstration of comparability is the cornerstone of a risk-based approach to lifecycle management.
- The objectives of the comparability exercise match the objectives of Quality by Design.
Comparability Assessments Offer a Risk-Based Approach to Post-Approval Lifecycle Management

• **Product Knowledge**
  – Critical attributes: what matters and why?
  – Structure-function understanding: Biological Characterization
  – Product stability profile: real-time and accelerated
  – Historical ranges

• **Process Understanding**
  – Link between process parameters and product quality attributes
  – Critical process parameters
  – Sources of variability (e.g. raw materials)

• **Structured, documented and disciplined approach to risk assessment and implementation**
Comparability Assessment

Key Steps

1. What’s changing?

2. What characteristics might be affected?

3a. How do we monitor the affected characteristics?
   - Justify the methods: R&D, validated, precision?
   - Do we also need data for unaffected characteristics to demonstrate consistency?

3b. Or, if no changes to characteristics are expected, what tests will confirm “no effect”?

4. What is the historical dataset?
   - Ranges, number of data points, statistics applied

5. Provide testing plan / design and data interpretation
   - Selection of comparator lots
   - Setting of acceptance criteria
Risk-Based Requirements for Comparability Exercise

Product Comparability Demonstrated by Analytical Testing
“Analytic Testing Only”

Product Comparability Demonstrated by A) and
Extended In Vitro Functional Testing
“Biological Characterization”

Product Comparability Demonstrated by A), B), and PK, PD or Tox Studies in Animals
“Animal PK or PK/PD Studies”

Extensive Comparative Human PK/PD and/or Safety Data Required
“Human Bioequivalency”

Additional Clinical Trials

Enhanced product and process knowledge is used
to design a rational comparability program

Consider for Early Dev, Less complex Late Stage/Commercial

Consider for Complex Late Dev/Commercial C
## Comparability Assessment

*Link comparability assessment to change-associated risk*

<table>
<thead>
<tr>
<th>Post-Approval Changes</th>
<th>Comparability Requirements</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Site change</strong>, no changes in characteristics</td>
<td>A</td>
</tr>
<tr>
<td><strong>Cell culture or recovery changes</strong>, no changes in characteristics</td>
<td>A (+B)</td>
</tr>
<tr>
<td><strong>Cell culture or recovery changes</strong>, with changes in charge distribution</td>
<td>A + B + C</td>
</tr>
<tr>
<td><strong>Cell culture changes</strong>, with changes in Fc glycan distribution (if Mab depletes cells)</td>
<td>A (+B)</td>
</tr>
<tr>
<td><strong>Formulation changes</strong>: API concentration, new excipients, or configuration change</td>
<td>A + B + [C] + D</td>
</tr>
<tr>
<td><strong>Switch from lyophilized to liquid form</strong>, increased minor forms, specification changes</td>
<td>A + B + [C] + E</td>
</tr>
<tr>
<td><strong>Route of administration change</strong></td>
<td>A + B + [C] + E</td>
</tr>
<tr>
<td><strong>New cell line</strong>, derived from original MCB or WCB by subcloning</td>
<td>A + B + [C] + D</td>
</tr>
<tr>
<td><strong>New cell line</strong>, from a new transfection or amplification or host</td>
<td>A + B + [C] + E</td>
</tr>
</tbody>
</table>

[C]- if a human study is conducted, an animal study may be superfluous and can be omitted
Analytical Testing *alone* is Appropriate for Minor Process Changes or Site Transfers

- Must meet all release and in-process specifications, as well as comparability acceptance criteria (e.g., tolerance intervals [TI, 95/99]) derived from **entire manufacturing history**

- Analytical profiles from selected characterization tests are consistent with pre-change material in side-by-side comparisons

- Extended characterization studies
  - Acceptance criteria established based on attribute monitoring not a part of the lot release system

- Process performance attributes must meet acceptance criteria

- Accelerated degradation profiles under stress conditions are consistent with pre-change material

- Real-time Drug Substance stability (as applicable; 0-6 months at time of submission)
## Comparability – Stability

### Stability Plans accepted by HAs (FDA & EMA) for DS changes

<table>
<thead>
<tr>
<th>Material</th>
<th>Lot description</th>
<th>Study Conditions</th>
<th>Study Data Required</th>
<th>Filing Package</th>
<th>Commitment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug substance</td>
<td>3x pre-and 3x post-change lots</td>
<td>40° C/75%RH (stressed)</td>
<td>14 days – 1 month</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>3x post-change lots</td>
<td>-20° C (recommended)</td>
<td>0 – 6 mo.*</td>
<td></td>
<td>Shelf life</td>
</tr>
<tr>
<td></td>
<td>3x post-change lots</td>
<td>5° C (accelerated)</td>
<td>0 – 6 mo.*</td>
<td></td>
<td>N/A</td>
</tr>
<tr>
<td>Drug product</td>
<td>1 lot filled from post-change DS</td>
<td>5° C (recommended)</td>
<td>Generally none*</td>
<td></td>
<td>Shelf life</td>
</tr>
</tbody>
</table>

- No real time or accelerated stability at the time of submission has been accepted by FDA with defined DS site changes – when stressed stability data meet pre-defined criteria. Commitment to add primary stability batches onto annual program
- No DP stability at the time of submission. Commitment to add primary stability batches onto annual program
Risk-based Comparability Strategies can Facilitate Risk-based Regulatory Strategies

Significant progress in scientific principles and associated regulatory framework achieved through open exchanges in Scientific Conferences, International Organizations and HA interactions.

- Development of regulatory guidance (ICH) and development of comparability study design
- Establishment of “Well-Characterized Biological” concept and conference
- Extensive use of comparability for single site, product changes with regulatory relief*
- Expansion of comparability to multiple simple changes (component simplification, bioreactor family…)
- Leverage QbD initiative to advocate for “expanded comparability/change protocols”
- 2011: First approvals of eCP across multiple facilities and products

Successful Global Approvals
- >20 drug substance site transfers
- 6 major process versions

* Reduced pre-approval category

Timeline ~ 18 YEARS
Risk-Based Regulatory Strategies Currently Available

**Standard Approach (US/EU)**

- Define CP, characterize and qualify the change
- Regulatory Filing (PAS, Type II, etc)
- Approval to market in ~6 months

**Accelerated Approach (US/EU) with Comparability/Change Protocol**

- Define CP
- Regulatory Filing (PAS, Type II, etc)
- Characterize and qualify the change
- Approval to market in 30 Days (CBE -30, Type Ib, etc)
Expanded Change Protocols (eCPs)

• Moves from one protocol for one discreet known change to an expanded protocol that can be applied to groups of similar changes to be executed at some future time

• Leverages existing regulations for change protocols

• A range of QbD concepts (ICH Q8, Q9, Q10, Q11) can be applied
  – Leverages historical knowledge
  – Systematic risk assessment and change requirements
Site Transfer of A Product Drug Substance Using A Comparability/Change Protocol

Drug Substance Donor Site X

Submit CP describing site transfer acceptance criteria for product-site combination

A B

Drug Substance Receiving Site Y

Product A

Execute transfer per defined requirements in CP

C A

CBE-30 Supplement with data demonstrating acceptance criteria met
Concept of eCP to Support Multi-Product, Multi-Site Transfers

A network of Drug Substance Donor Sites

Submit eCP describing acceptance criteria broadly for both Site and Product

Potential Future Network Requirements

Execute transfer per pre-defined requirements in eCP

CBE-30 Supplement with data demonstrating acceptance criteria met

A network of Drug Substance Receiving Sites

Site X or Z

Site X or Z

Site X or Y

Submit eCP describing acceptance criteria broadly for both Site and Product

Execute transfer per pre-defined requirements in eCP

CBE-30 Supplement with data demonstrating acceptance criteria met

Site Y or Z

Site X or Z

Site X or Z

Site X or Y
Multi-Site, Multi-Product eCP for DS Site-Transfers Accepted in FDA QbD Pilot Program for Biotech Products

Scope and Limitations

Site Transfer Risk Assessment

Comparability & Validation

Site Inspection

Criteria for establishing GMP/Compliance

Define how Product and Process will be Evaluated

Define facility/process modifications allowed

Risk-Based Approach to product/facility scope
Multi-Site, Multi-Product eCP for DS Site-Transfers: Outcomes

Scope: all Roche Bio-products and facilities, no CMOs

Agreed upon the risk assessment tools to ensure no major process changes were needed in order to “fit” the process into the new facility

Justified demonstration of comparability based on analytical DS data, process performance indicators and accelerated stability with post-approval real-time stability commitment

No requirement to demonstrate DP level stability

Agreed upon risk assessment tools to allow establishment of GMP compliance status so that PAI can be waived

Agreed future products and facilities could cross-reference the eCP if pre-defined scope criteria were met

Approved by FDA in 2011

Subsequent DS transfers approved under eCP criteria with CBE-30

Concept in development with EMA
Lifecycle Management Based on Modern Risk-based Concepts (ICH Q 5E, 8, 9, 10, 11, Draft WHO Guidelines)

- Initial BLA/NDA contains:
  - overall control strategy proposal including a design space proposal
  - A Post Approval Lifecycle Management (PALM) Plan with commitments to monitor product quality, process performance and verify changes within the design space

- Changes within the design space do not require pre-approval

- In some regions PALM is supplemented with: Comparability /Change Management Protocols to facilitate stream-lined regulatory management of planned changes outside the design space
  - Raw material changes
  - Site & scale changes
  - Working Cell Bank Replacements
  - Planned process improvements

- May add new product to existing approved expanded change protocols

*EMA has a similar structure with the use of Change Management Protocols
What is Needed to Ensure Continued Supply to Patients in a Expanding Global Marketplace

- Continued dialogue regarding realities of global manufacturing & supply
- Embrace and implement Risk based approach for product development and life-cycle management with emphasis on enhanced product and process knowledge and patient risk/benefit
- Continue to strive towards regulatory convergence and facilitate risk-based requirements and implementation timelines
Acknowledgements & Thanks To:

Wassim Nashebeh
Reed Harris
Kathy Francissen
Julia Edwards
Susanne Ausborne
Roche QbD Team
Doing now what patients need next