The Use of Comparability Protocols in Biologics: An Effective Tool to Manage Post-Approval Changes

Robin Levis, Ph.D.
Deputy Director, Division of Viral Products
Office of Vaccines Research and Review
CBER/U.S. FDA

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Disclaimer

The views presented here are the views of the speaker and should not be used in place of regulations, FDA guidances or discussions with the Agency.
Introduction

- Comparability and post-approval changes.
- Comparability protocols
Regulatory Guidance On Comparability

- CBER/CDER Guidance: Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products – 04/01/1996

- ICH Q5E: Comparability of Biotechnological/Biological Products Subject to Changes in their Manufacturing Process – June 2005

ICH Q5E Guidance

Guidance is intended to assist in the design and execution of studies used to collect the technical information to establish the comparability of pre-change and post changed product and thereby confirm that the manufacturing change(s) did not have an adverse impact on the quality, safety and efficacy of the drug product.
What is the basis for product comparability?

Before Licensure…

- Well defined product development pathway
  - Evolution of product and manufacturing process
    - Establishment of product quality characteristics
  - Influencing factors
    - Stage of product development
      - Extent of clinical data to support safety and efficacy
      - Experience with process and product
      - Degree of product characterization
      - Maturity of analytical methodology

- Well controlled clinical trial pathway
  - Accumulation of safety and efficacy data
    - Bridging/comparability of clinical data from each of the manufacturing processes throughout development

- Definition of manufacturing/clinical consistency
  - Lot to lot consistency as measured by quality control testing
  - Lot to lot consistency as measured by clinical attributes
...At licensure...

- Manufacturing process is validated and well controlled (facilities and product flow)
- Drug product is well characterized with well defined quality attributes
- Clinical data support that the product is safe and efficacious
...After Licensure

- After product licensure
  - Maintain product and clinical consistency
  - Rely on data from clinical and process development phases to support post-licensure changes
  - Often a rapid evolution of product and manufacturing process
    - Change in manufacturing scale
    - Change in manufacturing equipment
    - Change in manufacturing facility
    - Change in manufacturing process
    - Change in cell bank/virus seed
    - Change in product specifications
Data to demonstrate/support product comparability

- Have well defined product quality attributes

- Have validated procedures used to assay product characteristics

- Show that product manufactured after introduced changes is comparable – ultimately showing that the product will behave identically in the clinic (doesn’t necessarily mean a clinical study)

- Use above data to support the demonstration of comparability
Methodology to demonstrate product comparability

- Develop a well defined plan
- Research scale studies:
  - to identify any potential impact of desired process change on product quality
  - to identify necessary data needed to validate new process
- Assessment for the need to perform clinical studies to support comparability
- Validation studies:
  - manufacturing scale studies to demonstrate that product quality has not been negatively impacted by change in process

Note: Discuss all aspects with FDA prior to implementation
When is it necessary to include clinical data to support comparability?

- When the intended change may result in a change in the safety and efficacy of a product. Examples include:
  - Change in critical product quality attributes
    - Increase or decrease in potency limits
    - Major manufacturing process changes
  - Change in product composition
    - Excipients
  - Change in QC testing of critical quality attributes
    - Potency – change from *in vivo* to *in vitro* assays
Clinical trials post-approval

- Potential requirement for clinical study should be discussed with FDA
- Studies would typically be non-inferiority studies with the primary endpoint based on the measurable clinical expectations of the licensed product –
  - Look for potential AEs that may be related to product changes
  - Look at immunogenicity compared to product prior to implemented change
- Requirement for efficacy trial – may require new IND
Comparability Protocols
Changes to an approved application – 21 CFR 601.12(e) – Comparability Protocols

- Comparability Protocols are submitted and reviewed in the original BLA or as Prior Approval Supplements
- Protocol submitted should describe the nature of the change, tests, and acceptable limits
- Upon approval of the comparability protocol, subsequent supplements may have a reduced reporting category

- Also defined in 21 CFR 314.70(e) – Protocols
Regulatory Guidance On Comparability Protocols


- CBER/CDER Draft Guidance for Industry: Comparability Protocols for Human Drugs and Biologics: Chemistry, Manufacturing, and Controls Information
  - New draft of guidance available as of April 2016
Definition of Comparability Protocol

A comparability protocol is a comprehensive, prospectively written plan for assessing the effect of a proposed CMC post-approval change(s) on the identity, strength, quality, purity and potency of a drug product or a biological product (i.e., product), as these factors may relate to the safety or effectiveness of the product (i.e., product quality).
Regulatory submission of a Comparability Protocol

- May be submitted as part of an original BLA or after the approval as a supplement

- May be submitted as a one-time change or used repeatedly for a specified change over the lifecycle of a product

- May cover an identical change for multiple BLA applications
Examples of submissions of comparability protocols

- **In original BLA submission:**
  - For new master and working cell banks
  - For new master and working viral seeds
  - For extension of shelf life beyond the date approved at the time of licensure

- **After licensure:**
  - When repetitive changes are made to a single product (e.g., introduction of new products into an approved facility, addition of duplicate equipment, etc.)
  - When a single change is made across multiple products - trans-BLA (e.g., container closure system, QC assays)
  - When a single change is made for a single product
Use of a Comparability Protocol

Submission of a comparability protocol allows the agency to review:

- A description of one or more proposed CMC changes
- Analytical and risk assessment activities to support the intended change
- Plans to implement the change(s)
- A request for reduced reporting category when the data is submitted for review.
Submission and review of comparability protocols

A two-step process:

- Submission of a supplement (PAS) that contains a well-defined, detailed, written plan that describes changes covered by the protocol and specifies the tests and studies, analytical procedures and acceptance criteria
  - The supplement requires approval by the regulatory authorities before implementation of proposed changes

- Submission of the actual results/data based on the studies specified in the comparability protocol
  - A reduced reporting category will be designated if the results/data meet the pre-specified acceptance criteria
Submission and review of comparability protocols

IMPORTANT:

- If the activities specified in the approved comparability protocol are not performed or if the predefined criteria for success are not met, then any reduced reporting category is not justified and the change(s), if pursued, must be reported using the standard criteria as specified in the CFR and FDA guidance on post-approval changes.
Benefits offered by a CP

- Predefined regulatory expectations
  - Greater predictability regarding the expectations and timing of implementation
  - Shorter review time for implementation

- Will lead to a reduction of regulatory oversight:
  - Associated with reduced reporting category
  - Applicable to future changes
  - Additional information is less likely to be requested to support changes proposed under the protocol

- An opportunity for a more expedited product distribution
Draft Comparability Protocol Guidance

- Guidance describes the changes covered under a comparability protocol and tests and studies that will be performed, with predefined acceptance criteria that will be met to demonstrate that the CMC changes did not adversely affect the product.

- Details the relevant administrative issues involved in submitting a comparability protocol including recommended content

- Includes appendices with specific questions and answers related to experiences with comparability protocols
Draft Comparability Protocol Guidance

- Appendices:
  - General
  - Formulation (Component and/or Composition) Changes
  - Manufacturing Site Changes
  - Manufacturing Process Changes
  - Specification, Including Analytical Procedure (Methods), Changes
  - Packaging Changes
  - Process Analytical Technology Changes
Types of CMC changes submitted as comparability protocols

<table>
<thead>
<tr>
<th>CMC Changes (arranged in the order from most to least frequent)</th>
<th>Percentage</th>
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<tbody>
<tr>
<td><strong>Facilities/equipment-specific:</strong></td>
<td>~79%</td>
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<tr>
<td>• Facility renovation/upgrade</td>
<td>(trans-BLA dominate for this category of changes)</td>
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<tr>
<td>• Equipment qualification/upgrade</td>
<td></td>
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<tr>
<td>• Introduction of new products into a licensed area</td>
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<tr>
<td>• Site transfers (testing, filling, purification, etc.)</td>
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<tr>
<td><strong>Product/process-specific:</strong></td>
<td>~21%</td>
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<tr>
<td>• Process changes (e.g., scale-ups, purification, cell culture, etc.)</td>
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<tr>
<td>• Working Seed/Working Cell Bank Qualification</td>
<td></td>
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<tr>
<td>• Container/closure system</td>
<td></td>
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<tr>
<td>• Analytical methods</td>
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Summary

- Product comparability is a critical aspect of quality regardless of the type of post-approval change requested.
- Product and clinical development is where the foundation for assessing comparability starts.
- It is critical to have an understanding of the relationship between the quality attributes of your product and their impact on safety and efficacy.
- Comparability protocols offer a regulatory mechanism to expedite review and implementation of post approval changes.
- Critical to discuss the use of comparability protocols with the Agency.