A Regulatory Perspective on Biotechnology Product Comparability Protocols: On the Continuum between Traditional and Enhanced Approaches

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CMC Strategy Forum
Practical Use of Expanded Change Protocols
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Disclaimers

The views and opinions expressed should not be used in place of regulations, published FDA guidances or discussions with the Agency.
Outline of Today’s Presentation

• Summarize statute, regulations, and guidance relevant to comparability protocols
• Summarize DMA experience with comparability protocols highlighting the evolution of approaches
• Summarize OBP pilot program experience with expanded change protocols (eCP)
• Discuss examples of analytical capability which can support eCPs
• Discuss possible future applications of protocols
FD&C Act Chapter V:
Drugs and Devices

• “...a drug made with a major manufacturing change may be distributed only if, before the distribution of the drug as so made, the holder involved submits to the Secretary a supplemental application for such change and the Secretary approves the application.”
FD&C Act Chapter V: Drugs and Devices

• “…a major manufacturing change is a manufacturing change that is determined by the Secretary to have substantial potential to adversely affect the identity, strength, quality, purity, or potency of the drug as they may relate to the safety or effectiveness of a drug.”
Changes to an approved application

- Section 601.12(e) allows for the use of protocols “…describing the specific tests and studies and acceptance criteria to be achieved to demonstrate the lack of adverse effect for specified types of manufacturing changes…”
- “Any such protocols, or change to a protocol, shall be submitted as a supplement requiring approval from FDA prior to distribution…”
Guidance for Industry

Comparability Protocols -
Protein Drug Products and Biological Products
- Chemistry, Manufacturing, and Controls Information

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Submit comments on this draft guidance by the date provided in the Federal Register notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the Federal Register.

For questions regarding this draft document contact Christopher Jonecks (CHER) 301-435-5681, Stephen Moore (CDER) 301-827-6430, or Dennis Bensley (CVM) 301-827-6956.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Drug Evaluation and Research
Center for Veterinary Medicine
September 2003
Draft Guidance: Benefits of a CP

• “The use of a comparability protocol could allow an applicant to implement CMC changes and place a product in distribution sooner than without use of a comparability protocol.”
Draft Guidance: Changes inappropriate to a CP

• Nonspecific plans for CMC changes
• Changes for which the adverse effect cannot be evaluated by studies, tests, etc
• Changes that warrant submission of a new IND
• Changes that require S/E, nonclinical, PK/PD data
Draft Guidance: Basic Elements of a CP

• Description of planned change(s)
• Tests and Studies to be completed
• Analytical Procedures to be used
• Acceptance Criteria
• Proposed reporting category
mAb Approvals (cumulative) & Comparability Protocols

Calendar Year

Number

Cumulative Approved

Comp Protocols

CMC Supplements and Comparability Protocols

- Number of supplements received per calendar year:
  - 1995: 50
  - 1996-2000: 100
  - 2001-2005: 350
  - 2006-2010: 300
  - 2011-2012: 150

- Comparison protocols:
  - 1996-2000: 10
  - 2006-2010: 5
  - 2011-2012: 5
mAb CPs have been submitted for what purpose?

Before 2006
After 2005

Facility/Bldg/Location/Area
Manufacturing Process and/or Scale
Single Product to Multi-Product Facility
Analytical Method(s)
Office of Biotechnology Products (OBP) Pilot Program (FR notice 2008)

• In many cases, Comparability Protocols have been used for a single manufacturing change.

• Protocols based on quality-by-design submissions will focus on critical quality attributes related to chemistry, formulation, and process design.
Office of Biotechnology Products (OBP) Pilot Program (FR notice 2008)

• Such protocols will be referred to as Expanded Change Protocols. Expanded Change Protocols will describe the quality-by-design, risk based approach linking attributes and processes to product performance, safety, and efficacy.
ICH Q11
Manufacturing Process Development

Traditional
- Identify Potential CQA’s
- Define Manufacturing Process
- Define Control Strategy

Enhanced
- Systematic approach to evaluation and understanding
- Functional relationships that link material attributes and process parameters to CQAs
- Use of QRM to establish an appropriate control strategy which can include proposals for design space(s)

Slide courtesy of Betsy Fritschel, J&J
Sample ECP Q&A

• *Does the Agency agree that the strategy and outlined content proposed for the ECP are appropriate to support implementation of future process changes to the [drug name] drug substance manufacturing process...?*

• While the intent ECP is to allow for more expanded changes, your proposal to include undefined and significant process improvement changes is not supported by the product and process knowledge conveyed to the Agency.
Sample eCP comments

• A general principle as described in ICH Q5e is that the comparability assessment is related to the manufacturing change. Specifically:
  – “To identify the impact of a manufacturing process change, a careful evaluation of all foreseeable consequences for the product should be performed.”
Expanded Analytical Capability to Support eCP

• Improved/newer methods to better characterize / control some “foreseeable consequences”
  – Identify methods sensitive to change
  – Glycosylation profile method improvements
  – SVP: moving beyond <788>
  – Demonstrating stability profile equivalence
Consider Sensitivity of Methods to Distinguish Differences*

- pH
- Concentration (A280)
- SEC
- CEX
- cIEF
- SDS-PAGE
- cSDS
- Potency
- Peptide Mapping
- 2nd derivative near-UV
- Far-UV CD
- FT-IR
- Near-UV CD
- Intrinsic fluorescence
- Extrinsic fluorescence
- Dynamic light scatter
- SEC-MALS-QELS
- Differential scanning calorimetry

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Impact of Filling Pump on Particulates

“The results indicate that the rolling diaphragm Pump, peristaltic pump, and time-pressure Filler generated notably less protein sub-visible particles than the rotary piston pump.”

Nayak et al, J. Pharm Sci., Vol 100, 4198-4204 2011
Improved Glycosylation Analytical Methods

Strategies for the profiling, characterisation and detailed structural analysis of N-linked Oligosaccharides
Tharmalingam et al.
Glycoconjugate Journal
August 2012

The separation of human IgG N-glycans by HPLC (a) and UPLC (b). UPLC can baseline resolve 24 peaks in the IgG glycan pool.
ICH Q5e – Role of Stability Data in Comparability

• When considering the comparability of products, the manufacturer should evaluate, for example:
  – The need for stability data, including those generated from accelerated or stress conditions, to provide insight into potential product differences in the degradation pathways of the product and, hence, potential differences in product-related substances and product-related impurities;
Demonstrating stability profile equivalence

Plots of hx and new process slopes with EAC

From Sidor et al, BioPharm International, March 2011
ICH Q11 Example 2: Risk Ranking of Process Parameters

• A quality risk assessment utilising prior knowledge and development studies can be used to rank process parameters based on their relative potential to have an effect on product quality if parameter ranges were changed.

• The ranking of parameters from the quality risk assessment can be used to communicate with regulators regarding a lifecycle management approach to assure continual improvement throughout the product lifecycle.
ICH Q11 example 2: Risk Ranking of Process Parameters

• Initial Filing
  The histogram shows the potential impact to quality for future changes to parameter ranges based on the knowledge and understanding at the time of submission.

• Lifecycle Management Options for extension of ranges
  – Design Space
  – Proposal for management of changes
  – Managed by PQS without prior regulatory approval
Extension of ranges would normally initiate a regulatory post-approval change process.

The applicant can include in the original submission a proposal for extension of ranges for these parameters.

Extension of ranges is addressed primarily via the PQS (Q10).
Manufacturing Changes & Process Validation

• “A description of the planned change, a well-justified rationale for the change, an implementation plan, and quality unit approval before implementation must be documented (§ 211.100). Depending on how the proposed change might affect product quality, additional process design and process qualification activities could be warranted. Certain manufacturing changes may call for formal notification to the Agency before implementation, as directed by existing regulations…”
Summary & Conclusions

• Comparability protocols have a long history of successful implementation and have been applied to facility changes, process changes and method changes.

• Expanded change protocols have been discussed and implemented under OBP’s QbD Pilot program

• Enhanced understanding derived from utilization of targeted and up-to-date analytical capabilities can facilitate comparability protocols

• Comparability protocols can be part of long term product lifecycle management strategy
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References


