Comparability: Regulatory Considerations and Technical Challenges

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Outline

- Introduction
- General concepts for comparability
- Considerations for the comparability exercise
- Technical challenges from industry perspective

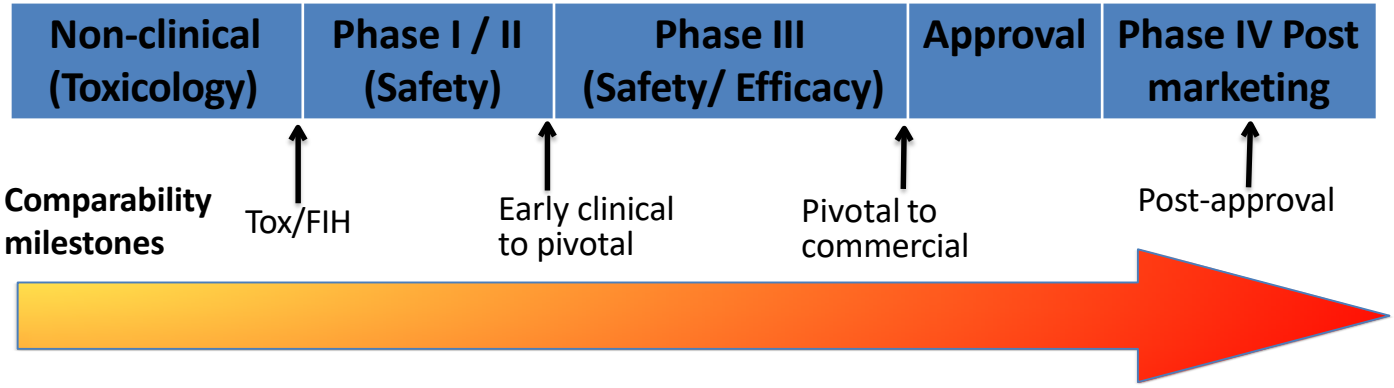
Disclaimer

The views and opinions expressed here represent those of the presenters only, and should not be used in place of regulations, published FDA guidance, or discussions with the Agency.

Phase appropriate comparability

Demonstration of comparability during development depends on:

- Stage of development
- Extent of the change(s) and potential impact on safety and efficacy
- Availability and suitability of analytical procedures
- Availability of pre-change material
- Extent of process and product knowledge (QTPP)



- *Scale up*
- *New manufacturing site*
- *Process improvement*
- *New cell bank*
- *Formulation/presentation changes*
- *Changes in analytical methods/quality controls*
- *Other changes (raw materials, equipment, storage and shipping)*

Comparability: Regulatory Considerations

"The demonstration of comparability does **not** necessarily mean that the quality attributes of the pre-change and post-change product are **identical**, but that they are *highly similar** and that the existing knowledge is sufficiently predictive to ensure that any **differences** in quality attributes have **no adverse impact** on safety or efficacy of the drug product."

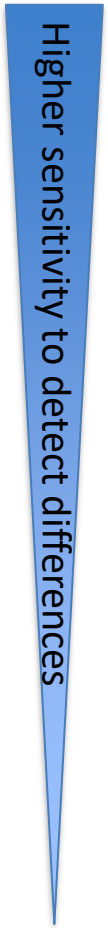
* As defined in ICH Q5E (emphasis added)

Importance of analytical comparability

Analytical
- Structure
- Function
- Impurity Profile
- Molecular Heterogeneity
- Stability

Non-clinical
- Toxicity
- PK/PD
- Tissue Cross Reactivity

Clinical
- PK/PD
- Safety and Efficacy
- Immunogenicity



- If a manufacturer can provide assurance of comparability through analytical studies alone, non-clinical or clinical studies with the post-change product are not warranted

- However, where the relationship between specific quality attributes vs. safety and efficacy has not been established, additional studies such as non-clinical and/or clinical may be needed to address the observed differences in quality attributes between the pre- and post-change product.

ICH Q5E

Comparability Exercise: Quality Considerations

Analytical Techniques
- Battery of tests
- Orthogonal tests for CQAs
- Modify or add new tests

Characterization
- Physicochemical properties
- Biological activities
- Immunochemical properties
- Purity, impurities, contaminants

Specifications
- Phase appropriate
- Data within specification but outside of historical trend
- Justify changes in the tests

Stability
- Real-time stability
- Accelerated and stressed (degradation rates/pathways)
- Justify the stress conditions

Comparability assessment should be based on totality of the data and information.

Comparability Protocol
- Postapproval Change Management Protocol (PACMP)

- A comprehensive, prospectively written plan for assessing the effect of a proposed post-approval CMC change(s) on the identity, strength, quality, purity, and potency of a product, as these factors may relate to the safety or effectiveness of the product (i.e., product quality) – FDA Guidance (Oct 2022)

- Specify the nature of the change, specific tests and studies to be performed, and acceptance criteria to be achieved per 21 CFR 601.12(e) and 21 CFR 314.70(e)
  - Tests and studies should be performed at manufacturing scale and use a combination of routine quality controls (specs, process controls, annual stability) and non-routine tests (characterization /additional stability studies)
  - Requires extensive knowledge of the product and manufacturing process

- Submitted and reviewed as part of the original BLA or as a Prior Approval 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 (trans-BLA)

- Upon approval, subsequent supplements **<u>may</u>** have a reduced reporting category

Comparability Guidances

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

- CBER/CDER Guidance: Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products (April 1996)

- CBER/CDER Guidance: Comparability Protocols for Postapproval Changes to the Chemistry, Manufacturing, and Controls Information in an NDA, ANDA, or BLA (October 2022)

Comparability Technical Challenges

Comparability Technical Challenge: Setting Meaningful Acceptance Criteria

- Phase Appropriate considerations in order to set meaningful ACs
  - Pre-pivotal leveraging clinical specification
  - Pivotal and Commercial leveraging statistical analysis for specification methods
    - Limit pre-change changes = challenges with statistics alone
    - Acceptance criteria using statistical analysis are too tight or wide = not meaningful

- Moving towards a holistic approach for setting ACs
  - Numerical Reported Results
  - Visual comparison of purity profiles (chromatograms and electropherograms)
  - Structure Function Relationship

  - When Numerical Criteria <u>is met:</u>
    - An atypical (eg in chromatogram profile), this would still require investigation and thorough evaluation.

  - When Numerical Criteria <u>not met:</u>
    - A thorough investigation and a root cause analysis would be performed to understand the difference. If the difference is not expected to impact safety or efficacy this justification would be provided to justify the difference and deem the materials comparable.

Questions for Discussion

1. How do you develop comparability study strategy, for example – key elements of the risk framework and phase-dependent considerations?
2. Testing strategy: How do you balance analytical method toolbox needed to demonstrate pre and post change materials are comparable?
3. Challenges in setting meaningful acceptance criteria: What are the strategies used for setting acceptance criteria for early stage/late stage, or for low volume products with limited manufacturing history? Are there considerations in case of criterion failure and assay limitations?
4. Demonstration of comparability in the marketing application: How would you present the data from earlier (i.e. pre-pivotal) comparability in the dossier?
5. Are there key learnings/experiences with Comparability Protocol/PACMP that can help support comparability discussion with HAs, to facilitate and/or accelerate the review of major changes?

BACK UP

Developing a Comparability Strategies

- Move away from throwing the analytical toolbox at the pre- and post- change samples.

- Leverage a decision tree/risk assessment to design the study
  - What quality attributes are expected to be impacted by the change?
  - Does the quality attribute(s) adversely impact or potentially adversely impact safety or efficacy?
  - What analytical methods are available to measure the attributes?
  - Batch Analysis, Extended Characterization, Force Degradation, Stability

- Tailor the strategy to measure the attributes which are impacted and the phase of development.
  - Changes in early phase with minimal impact to quality attributes = smaller study
  - Large Changes (site, media change, new formulation) in pivotal or commercial = larger more compressive study

Analytical Toolbox

- Release and Shelf-life Specification Methods vs. Characterization Methods
- Phase Appropriate Testing Strategy
- What quality attributes are different between pre-change and post- change

Points to consider when setting meaningful Comparability ACs with limited pre-change data

- Having consistent and objective approach to evaluate comparability using a holistic data set is more important than setting and meeting these quantitative ACs (often derived statistically)
  - Even if ACs are met and if there is something atypical (eg in chromatogram profile), this would still require investigation and thorough evaluation.
  - On the contrary, if an attribute did not meet the predefined quantitative AC but a thorough investigation and RCA was conducted to justify the difference, it can be acceptable.
- Phase appropriate consideration in order to set meaningful ACs
  - Early/late or launch stages where the product is not yet on the market - the focus of comparability is on the evaluation approach (ie align with ICH expectation), and may need to be supported by other data, e.g. minor variant characterization, non-clinical studies to broaden understanding of charged variant impact on pK
  - For commercial products, there's a high bar to comparability approach in order to maintain the product quality and safety profiles which may require stringent ACs. Therefore, HAs may scrutinize ACs if CP/PACMP are being submitted ahead of the comparability executions.
  - Legacy products where batches with clinical exposure are limited continue to pose challenges to set meaningful ACs. Additionally, the challenge is greater as control system evolves over the life of products.

Slides by Ivy Lin and Helen Kumagai

Comparability Protocol/PACMP

Defining the approach to setting acceptance criteria (i.e. 95% Tolerance Intervals) versus providing the numerical limits.

When filing a PACMP a sufficient number of pre-change batches may not yet be manufactured to set the numerical acceptance criteria.

Providing the approach to setting the acceptance criteria would allow a company to file the PACMP while the pre-change batches are being manufactured.

Comparability in Marketing Application

Toxicology, All Clinical Processes and Commercial

- Tabular Numerical Side by Side Comparison
- Visual Comparison of spectra, chromatographs, electropherograms

Latest Comparability Study

- Tabular Numerical Side by Side Comparison
- Visual Comparison of spectra, chromatographs, electropherograms

Previous Comparability Study or Studies

- Tabular Numerical Side by Side Comparison

Pivotal Comparability Study

- Tabular Numerical Side by Side Comparison
- Visual Comparison of spectra, chromatographs, electropherograms