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A Regulatory Perspective on Methods Used for Analytical Similarity Assessments

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This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Presentation Overview

- Background
- Expectations for analytical similarity methods
  - Method qualification/validation
  - Data analysis
- Case studies
- Additional insight
- Conclusions

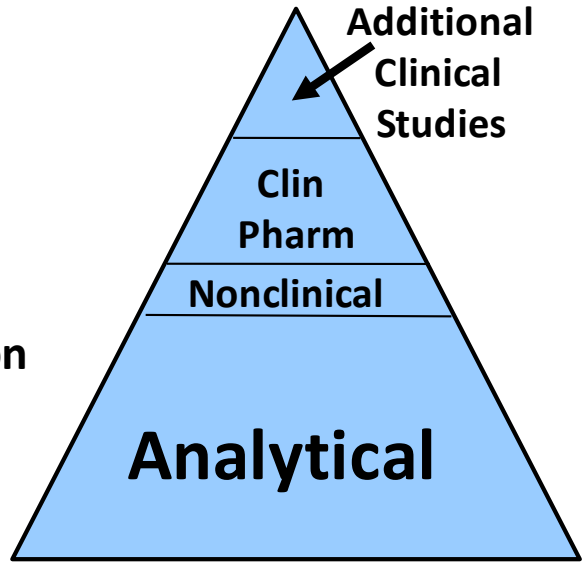
351(k) Biosimilar Pathway

- An abbreviated licensure pathway for biological products shown to be biosimilar to an FDA-licensed biological product ("reference product")
- Biosimilar/Biosimilarity – "the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components," and that "there are no clinically meaningful differences between the biological product and the reference product in terms of safety, purity, and potency of the product"
- 351(k) application must contain, at least, data derived from analytical studies, animal studies, and a clinical study or studies, unless otherwise determined by the FDA
- The totality of the evidence submitted is considered when evaluating a demonstration of biosimilarity between the proposed product and the reference product

Analytical Similarity: Foundation to Demonstrating Biosimilarity

"FDA expects that first, a sponsor will extensively characterize the proposed product and the reference product with state-of-the-art technology, because extensive characterization of both products serves as the foundation for a demonstration of biosimilarity."—Scientific Considerations in Demonstrating Biosimilarity to a Reference Product

- **Stepwise approach starting with extensive structural and functional characterization**
- **Allows an evaluation of the analytical differences between the proposed biosimilar and the reference product, and any resulting residual uncertainty**
- **Identify next steps to try to address that uncertainty**
  - **Orthogonal methods to further evaluate impact on function**
  - **Control strategies to minimize the differences**
  - **Nonclinical**
  - **Clinical**



Analytical Similarity Assessment Considerations

Structural
- Primary structure
- Higher order structure
- Molecular weight
- Heterogeneity

Functional
- Biological activity
- Enzyme kinetics
- Target binding
- Fc effector functions

Product-related variants
- Size-related variants (aggregates, fragments)
- Glycosylation variants (nature, location, and level)
- Oxidation variants
- Charge-related variants
- Sequence variants
- Disulfide linkage variants

Stability
- Degradation profiles under accelerated stress (high temperature, freeze-thaw, light exposure, agitation), forced conditions

Impurities and product-related attributes
- Process-related impurities (host cell protein and DNA, etc.)
- Subvisible particles
- Protein concentration

Example Analytical Methods

Structural
- LC-ESI-MS/ESI-TOF-MS
- FTIR
- CD (Far-and Near-UV)
- DSC
- Intrinsic fluorescence

Functional
- Cell-based bioassay
- SPR
- AlphaScreen
- ELISA

Product-related variants
- CEX-HPLC
- icIEF
- SE-HPLC
- CE-SDS (reducing and non-reducing)
- HILIC
- SV-AUC
- SEC-HPLC/MALLS

Stability
- Stability indicating assays:
  - potency
  - SE-HPLC
  - CD-SDS
  - CEX-HPLC

Impurities and product-related attributes
- ELISA
- LC-MS
- 2D-DIGE
- qPCR
- UV
- MFI

Expectations for Analytical Similarity Methods

- State-of-the art, quantitative methods
- Should be selected based on the nature and understanding of the proposed product and the reference product (e.g., knowledge of structure, heterogeneity, critical quality attributes)
- Capable of detecting differences between the proposed biosimilar product and the reference product
- Inclusion of orthogonal methods
- Method qualification or validation data demonstrating that the assay is suitable for the intended purpose

Validation or Qualification of Analytical Similarity Methods

> *"Unlike routine quality control assays, tests used to characterize the product do not necessarily need to be validated."*—Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product

The analytical data generated using these methods are the foundation for biosimilar development and may be used in lieu of a full clinical program. Therefore, these methods should be:

- Well-developed
- Scientifically sound
- Demonstrated as fit for intended use
- Capable of providing reproducible and reliable results

Typically see both qualified and validated methods in the analytical similarity assessment.

Analytical Method Qualification

- Determines whether an assay is suitable for its intended purpose
- Qualification studies will identify/refine method performance capabilities such as specificity, linearity, accuracy, precision, robustness, stability etc.
- Can provide a sufficient foundation for the development of a scientifically sound validation study
- Limited pre-determined method performance specifications
- A method typically will not fail qualification; it gets re-optimized until it can achieve acceptable performance or it is rejected for the intended study
- Typically conducted in a research and development (R&D) environment

Analytical Method Validation

- Assuring an assay is suitable for its intended purpose on a routine basis
- Validation studies are run according to an established validation protocol
- Method performance specifications are pre-established, documented, and confirmed during validation trial
- These specifications must be met to support validation
- A method can fail validation; if it does, assignable cause for the failure must be investigated, resolved, and the assay re-validated
- Typically conducted in a quality controlled (QC) environment

Analytical Similarity Method Validation or Qualification?

- Consideration should be given to developing and conducting critical analytical similarity methods in a QC environment
  - For licensure, methods used in the analytical similarity assessment may be added to the overall product control strategy and be implemented at release or on stability
- Well documented assurance of method qualification/validation, data collection, and analysis will be reviewed as part of a 351(k) submission, and during pre-licensing inspection (analytical similarity focus)

Extent of analytical similarity method information to be included in the 351(k) submission

- Method descriptions
- Summaries of method performance
  - System suitability criteria
  - Qualification/validation parameters evaluated
  - Detailed summaries are useful in interpreting analytical similarity data
- Location (i.e., lab, facility) where analytical similarity data were generated
- Method transfer data, as applicable, if assay is developed outside of the analytical similarity assessment testing site
- Bridging data, as applicable, when different methods were used to evaluate the same quality attribute and data from both methods are combined and reported in the application

Data Analysis, Collection and Reporting

- Data analysis should be consistent and purposeful
  - Use of appropriate reference standards (qualified, properly stored, internal assay controls)
  - Use of proper integration methods
  - Audit trails
  - Consistency in rounding
  - Consistency in use of geometric or arithmetic mean

- Collection and reporting of data
  - Electronic or paper laboratory books and reports
  - Ensure data is properly analyzed and reported in the application

Case Study 1: Cell-based bioassay method development

- Product: proposed biosimilar to an FDA-approved monoclonal antibody
- Cell-based bioassay developed and validated to evaluate potency based on the recognized mechanism of action of the reference product and proposed biosimilar
- A modification of the reference product is known to impact potency
- Analytical similarity data show no impact on potency for either the reference product or proposed biosimilar when evaluating a protein fraction thought to be enriched with the modification

Case Study 1: Cell-based bioassay method development

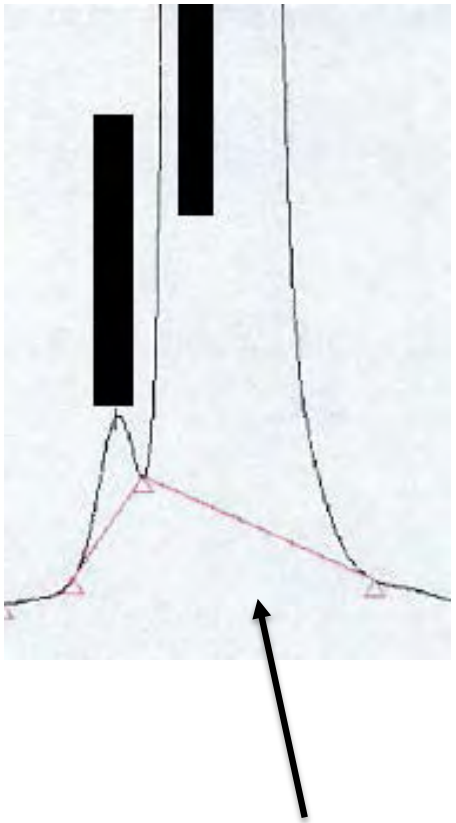
- Questions:
  - What does this say about the assay sensitivity?
  - Can the assay reliably detect differences in potency between the proposed biosimilar and the reference product?
  - Can these data be used to support analytical similarity?
- Evaluation of the modification using an alternative method was requested
  - Qualification/validation data for the alternative method
  - Data comparing a sufficient number of reference product lots and proposed biosimilar lots using the alternative method

Case Study 2: Chromatography data analysis

- Product: proposed biosimilar to an FDA-approved therapeutic protein

- Data analysis by analysts resulted in inconsistent reported results
  - Standard operating procedure was unclear on how to conduct peak integration and did not enable an adjustment of the baseline
  - A substantial portion of the peaks were unaccounted in the reported result

- Resulted in variable analytical similarity data and a misinterpretation of the comparative forced degradation results



Case Study 3: Enhanced data analysis

- Product: proposed biosimilar to an FDA-approved monoclonal antibody
- During a pre-licensure data audit, analytical similarity data reported in the application were compared to the analytical data reports at the firm
- Differences were noted in the % peak areas reported for various glycosylation species between the data submitted in the 351(k) and the original data generated at the firm
- Following detailed discussions with subject matter experts, it was revealed that the original data were reintegrated based on an improved understanding of the peaks/peak identification
- All of the data were reevaluated and submitted to the application
- The improved peak identification lead to a more comprehensive glycosylation profile and understanding of the proposed product and reference product

Additional Insight

- Pre-licensing inspections may be conducted focused on auditing the analytical similarity data submitted in a 351(k) BLA under review
  - Subject matter experts and analyst should be available to discuss methods and data analysis
  - Original data reports and raw data available for the proposed biosimilar and reference product lots
  - Data handling, reporting and archiving may be audited
  - Reference product tracking and storage
- Additional considerations
  - Ensure that data reported in the analytical similarity assessment are correct, clear, and sufficient to provide confidence in the data and facilitate an adequate product quality review
  - A robust analytical similarity assessment is critical to the overall biosimilarity determination, and a robust process characterization and product understanding is paramount to define an appropriate control strategy for BLA approval

Conclusions

- A robust analytical similarity program that includes in-depth structural and functional characterization improves the likelihood that any analytical differences between highly similar products can be addressed

- To achieve this, well-developed, state-of-the-art, scientifically sound methods should be employed

- Sufficient information and data should be provided to demonstrate that the methods are suitable for the intended purpose

- Ensure proper documentation of method qualification/validation, data analysis, and data reporting in case of a data audit

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