FDA Perspectives on Biosimilar Biologic License Applications- Manufacturing Biosimilars

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Learning Objectives

- Overview of 351(k) pathway
- To understand the Agency's expectations for manufacturing of biosimilar products at licensure
- Identify potential road blocks to approvability related to the manufacturing of biosimilar products

Background

- The **Biologics Price Competition and Innovation Act of 2009 (BPCI Act)** was passed as part of health reform (Affordable Care Act) that President Obama signed into law on March 23, 2010.

- BPCI Act creates an ***abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with*** an FDA-licensed reference product.

What is an Abbreviated Licensure Pathway for Biological Products?

A licensure pathway that permits a biosimilar biological product to be licensed under 351(k) of the Public Health Service Act (PHS Act) based on **less than a full complement of product-specific preclinical and clinical data** → **abbreviated** licensure pathway**.**

- A biological product that is demonstrated to be "***highly similar***" to an FDA-licensed biological product (the reference product) may rely for licensure on, among other things, comparative clinical data and publicly-available information regarding FDA's previous determination that the reference product is safe, pure and potent.

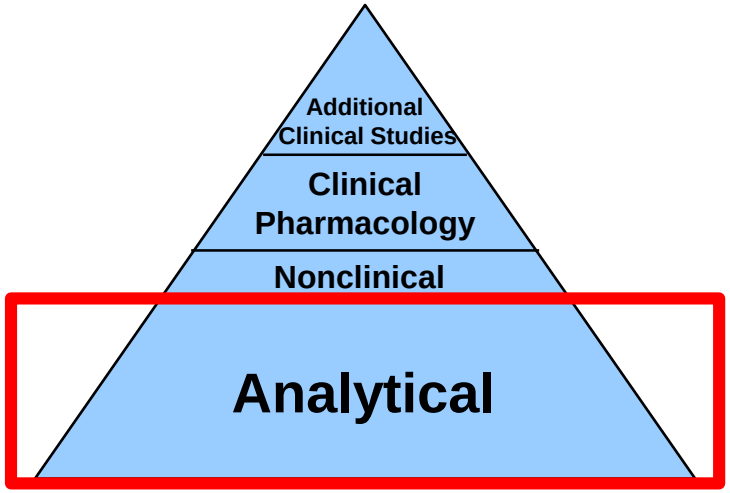
Definitions

Biosimilar or **Biosimilarity** means:

- that the biological product is **highly similar** to the reference product notwithstanding minor differences in clinically inactive components; and

- there are **no clinically meaningful differences** between the biological product and the reference product in terms of the safety, purity, and potency of the product.

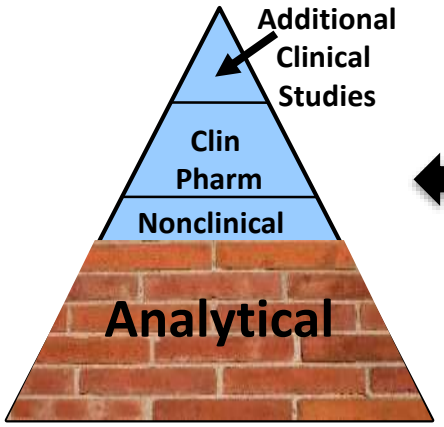
Analytical Similarity: Foundation of the Biosimilar Program



"Abbreviated" Development Program, 351(k) BLA

- Understand the molecule and its function
- Extensive structural and functional characterization
- Identify critical quality attributes and clinically active components
- Understanding the relationship between quality attributes and the clinical S & E profile aids ability to evaluate residual uncertainty and assess what additional studies might be needed

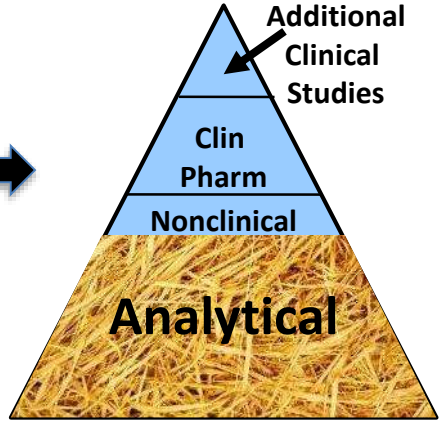
A foundation must be solidly built to support the program



YES

- ✓ Data for biosimilar and reference product submitted to BLA are representative and accurate
- ✓ Sound analytical methods
- ✓ Consistent reference standards
- ✓ Robust sample handling
- ✓ Robust data handling
- ✓ Well documented

NO



General Requirements: 351(k) Applications

351 (k) BLA:
The PHS Act requires information demonstrating biosimilarity based on data from:

- **Analytical studies** demonstrating that the biological product is "highly similar" to the reference product notwithstanding minor differences in clinically inactive components.
- **Animal studies** (including the assessment of toxicity)
- A **clinical study or studies** (including the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD)) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the reference product is licensed and for which licensure is sought for the biosimilar product.

Challenge Question

- True or False? Given the additional analytical assessments and abbreviated clinical and non-clinical programs, manufacturing development for proposed biosimilars can also be abbreviated?

False

Certain requirements of 21 CFR 600 and 21 CFR 211 must be met: the information needed to support product purity, potency and safety **is not abbreviated**

Expected CMC packages in 351(k) BLA submissions

- **Robust** analytical similarity assessment

- Data and information supporting that the manufacturing **consistently** delivers a product that **meets** the intended purity, potency, safety and stability characteristics

- Manufacturing facilities that are GMP compliant

State of the Biosimilar Program

- **As of October 1, 2019, 73 programs** were enrolled in the Biosimilar Product Development (BPD) Program. CDER has received meeting requests to discuss the development of biosimilars for **38** different reference products.
- FDA is prohibited from publicly disclosing the existence of a pending application, unless the existence of the application has been previously publicly disclosed or acknowledged, because this information is confidential and belongs to the manufacturer/sponsor developing the drug.
- Since program inception and as of **October 1, 2019**, **12** companies have publicly announced submission of **30** 351(k) BLAs to FDA.
- **Twenty-three** 351(k) BLAs for biosimilar products have been approved.
  - Zarxio (filgrastim-sndz) – Approved 3/6/15 (Neupogen)
  - Inflectra (infliximab-dyyb) – Approved 4/5/16 (Remicade)
  - Erelzi (etanercept-szzs) – Approved 8/30/16 (Enbrel)
  - Amjetiva (adalimumab-atto) – Approved 9/23/16 (Humira)
  - Renflexis (infliximab-abda) – Approved 4/21/17 (Remicade)
  - Cyltezo (adalimumab-adbm) – Approved 8/25/17 (Humira)
  - Mvasi (bevacizumab-awwb) – Approved 9/14/17 (Avastin)
  - Ogivri (trastuzumab-dkst) – Approved 12/1/17 (Herceptin)
  - Ixifi (infliximab-qbtx) – Approved 12/13/17 (Remicade)
  - Retacrit (epoetin alfa-epbx) – Approved 5/15/18 (Epogen)
  - Fulphila (pegfilgrastim-jmdb) – Approved 6/4/18 (Neulasta)
  - Nivestym (filgrastim-aafi) – Approved 7/20/18 (Neupogen)
  - Hyrimoz (adalimumab-adaz) – Approved 10/30/18 (Humira)
  - Udencya (pegfilgrastim-cbqv) – Approved 11/2/18 (Neulasta)
  - Truxima (rituximab-abbs) – Approved 11/28/2018 (Rituxan)
  - Herzuma (trastuzumab-pkrb) – Approved 12/14/18 (Herceptin)
  - Ontruzant (trastuzumab-dttb) – Approved 1/18/2019 (Herceptin)
  - Trazimera (trastuzumab-qyyp) – Approved 3/11/19 (Herceptin)
  - Eticovo (etanercept-ykro) – Approved 4/25/2019 (Enbrel)
  - Kanjinti (trastuzumab-anns) – Approved 6/13/19 (Herceptin)
  - Zirabev (bevacizumab-bvzr) – Approved 6/27/19 (Avastin)
  - Ruxience (rituximab-pvvr) – Approved 7/23/19 (Rituxan)
  - Hadlima (adalimumab-bwwd) – Approved 7/23/19 (Humira)

Issues that impact approvability

- Analytical similarity
  - Inadequate reference standard qualification
  - Inadequate characterization of critical attributes (e.g. impurities that affect potency, glycan structures)
- Product quality
  - Control strategy
  - Routine manufacturing
  - Facilities

Challenge Question

- True or False? Most of the approvability issues that the Agency sees with biosimilar applications is due to the inability to demonstrate that the proposed biosimilar is highly similar to the reference product?

False

Reference Standards

- Appropriately qualified reference standards are critical for analytical similarity assessment and release of biosimilar products lot:
  - Adequate bridging studies are needed when using multiple reference standards, particularly at the beginning of the biosimilar program, when lots of US-licensed reference product or non-US approved comparator may be used
  - Establish an in-house reference standard as soon as feasible
  - A two-tier reference standard system, with primary and working reference standard should be available at the time the BLA is submitted, with appropriate qualification protocols
  - Appropriate qualification:
    - Adequate number of replicates for assays that have higher variability (e.g. potency assays) for both release and analytical similarity
    - Pre-determined confidence interval of the mean, where the mean relative potency and the 95% confidence interval (CI) are included within a sufficiently narrow range (90-110%) and the CI is not repeatedly on one end of the 90-110% range.
    - Assign 100% potency; correction factors are discouraged. Evaluate multiple lots and select one that closely match the reference standard
    - Establish a monitoring program, adequately justified

Analytical studies

- Forced degradation studies are an important element in establishing analytical similarity. All important assays should be included in these studies
- Impurity profiles and individual impurities should be characterized and compared to the reference products
- Assays should be demonstrated to be suitable for the intended use

Example: 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 when using the cell-based assay
- **Challenge Question: Would this assay be acceptable for release and stability testing?**

Evaluation of the modification using an orthogonal method was requested

Analytical methods

- Analytical methods must be appropriately validated/ qualified and demonstrated to be suitable for the intended purpose
- Acceptance criteria chosen to provide meaningful information
  - Identity: conform to reference standard?
- Methods can be improved or changed during development depending on necessity and additional information
- Methods can be transferred to a new site

Case study 2: Change to analytical method

- Applicant switched from method 1 to method 2 during development
- Stability data generated with both methods
- Inadequate data to support comparable performance of method 1 and 2

Change to analytical method expectations

- Methods should be adequately bridged to demonstrate comparable performance
  - Use of retain samples where feasible
  - Use of appropriate materials (e.g. samples containing varying levels of impurities)
- Similar approaches should be used when a method is transferred to a new site
  - Provide method transfer report in the BLA

Frequently Missing or Incomplete Manufacturing Data

- Adequate qualification of data and information supporting the validity of scale down models
- Adequate validation data supporting removal of process related impurities
  - Studies conducted to demonstrate removal should include worse case scenario (e.g., spiking studies)
  - Cell bank information: characterization, stability, use in manufacture
    - Monitoring program at appropriate intervals with adequate controls
    - End of Production cells: population doubling
    - Cell bank qualification protocols: at scale manufacturing of at least on lot
- Information on critical raw materials and studies to support their use (e.g., polysorbate stability)

Frequently Missing or Incomplete Manufacturing Data

- Data and acceptance criteria supporting column and membrane reuse and adequate protocol to extend use cycles
- Leachable and extractable studies for product contact surface: risk assessment and pertinent data and information
- Adequate stability data supporting critical steps: hold times for intermediates, buffers, inclusion bodies
- Stability studies conducted in representative container closure systems (e.g., plastic vs stainless steel)

Release and stability

- Release and stability program are critical to ensure the product maintains the quality characteristics it is purported to possess
  - Appropriately validated assays
    - Sensitive, precise and accurate
    - Demonstrate capability of detecting degradants (for stability purposes)
  - Appropriately selected attributes
    - Relevant for clinical performance (safety and efficacy)
    - Mechanism of action
  - Appropriately selected acceptance criteria
    - Supported by clinical studies
    - Representative of the manufacturing process
    - Consideration of the reference product

Facilities inspections

- Inspection of facilities during the review cycle is a key component for licensure of a new product
  - 21 CFR 601.20-Biological licenses; issuance and conditions…*(b) Availability of product.* No biologics license shall be issued unless :
    - (2)such product is available for inspection during all phases of manufacture
  - 21 CFR 600.21 Time of inspection
    - The inspection of an establishment for which a biologics license application is pending need not be made until the establishment is in operation and is manufacturing the complete product for which a biologics license is desired...
  - Manufacturing schedule that allows for inspection in a reasonable time frame for completion of review activities

Inspectional issues

- Data traceability and discrepancy between on-site data and data submitted in the licensing application
- Inadequate environmental monitoring
- Inadequate media fill strategies
- Inadequate aseptic procedures
- Quality agreement with contract manufacturing organizations should clearly define role, responsibilities and oversight

A pitch for immunogenicity

- Immunogenicity is a critical component of the biosimilar program, needed to support a determination of biosimilarity
- CMC reviewers review immunogenicity assays
  - Deficiencies in assay development and validation are frequent review issues
- Recommendation: obtain agreement on assays from the Agency **before** testing clinical samples

Conclusions

- Analytical similarity packages are, with few exceptions, adequately prepared and support a determination of highly similar
- Inability to receive approval for a biosimilar BLA is more often the result of submitting inadequate manufacturing information or facility issues
- BPD meeting are not solely devoted to discussion of analytical similarity
  - Reaching out to the Agency with specific questions aimed at asking advice on manufacturing is in scope

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