Regulatory Expectations: Biosimilars and Biologics

2017 AAM Biosimilars Council Conference
Washington DC.

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Overview

- Biosimilars
  - Overview BPCI Act and FDA guidance
  - General requirements
  - Development
    - CMC
- Clarification on Expectations for Biologics License Applications

Overview of the BPCI Act

Background

- The **Biologics Price Competition and Innovation Act of 2009 (BPCI Act)** was 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.
  - 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, publicly-available information regarding FDA's previous determination that the reference product is safe, pure and potent.
  - This licensure pathway 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**.**

What is Meant by Abbreviated Licensure Pathway?

- The abbreviated licensure pathway **does not mean that a lower approval standard** is applied to biosimilar or interchangeable products than to originator biological products.

- The ability to rely on FDA's previous finding regarding the reference product to support approval of the biosimilar product allows for a potentially shorter and less costly drug development program. This is what is meant by an **abbreviated** licensure pathway.

- The **data package** required for approval of a biosimilar or interchangeable product is quite extensive; biosimilar applicants submit data from analytical, nonclinical, and clinical studies to support a demonstration of biosimilarity with the reference product.

Biosimilarity

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.

Reference Product

Reference Product:

- the **single biological product, licensed under section 351(a) of the PHS Act,** against which a biological product is evaluated in an application submitted under section 351(k) of the PHS Act.

- Data from animal studies and certain clinical studies comparing a proposed biosimilar product with a non-US-licensed product may be used **to support** a demonstration of biosimilarity to a US-licensed reference product.

  - Sponsor should provide adequate data or information to **scientifically** justify the relevance of these comparative data to an assessment of biosimilarity and to **establish** an **acceptable bridge** to the U.S.-licensed reference product.

General Requirements

A 351(k) application must include information demonstrating that the biological product:

- Is **biosimilar** to a reference product;
- Utilizes the **same mechanism(s) of action** for the proposed condition(s) of use -- but only to the extent the mechanism(s) are known for the reference product;
- **Condition(s) of use** proposed in labeling **have been previously approved** for the reference product;
- Has the **same route of administration**, **dosage form**, and **strength** as the reference product; and
- Is manufactured, processed, packed, or held in a facility that **meets standards** designed to assure that the biological product continues to be safe, pure, and potent.

General Data Elements : 351(k) Application

The PHS Act requires that a 351(k) application include, among other things, **information demonstrating biosimilarity based upon data derived 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); and
- 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.

FDA may determine, in its discretion, that an element described above is unnecessary in a 351(k) application.

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Overview of FDA's Approach to the Development of Biosimilars

Key Development Concepts

FDA Guidance

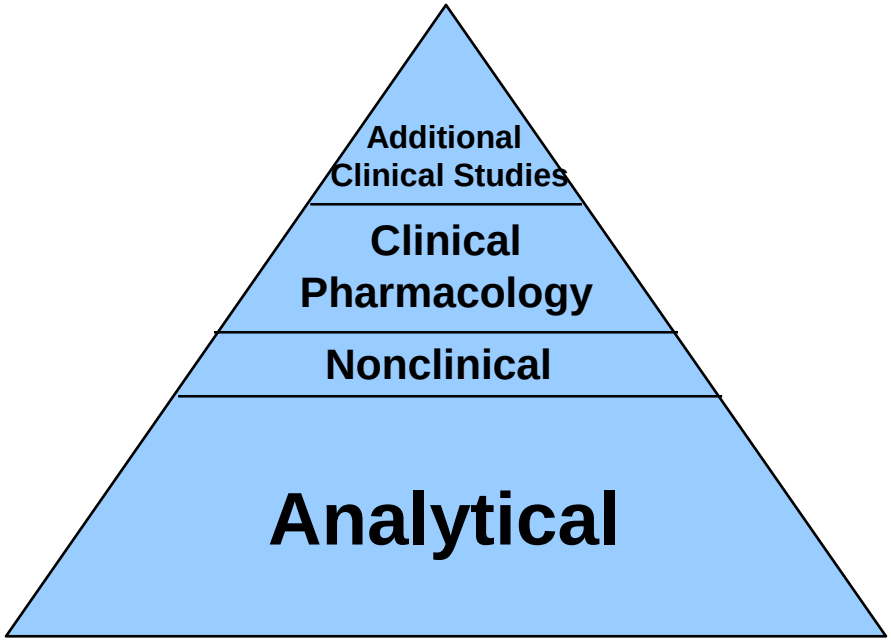
1. **Scientific Considerations in Demonstrating Biosimilarity to a Reference Product (final, 2015)**
2. **Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product (final, 2015)**
3. **Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (final, 2015)**
4. **Formal Meetings Between the FDA and Biosimilar Biological Product Sponsors or Applicants (final, 2015)**
5. **Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product (final, 2016)**
6. **Nonproprietary Naming of Biological Products (final, 2017)**
7. Reference Product Exclusivity for Biological Products Filed Under Section 351(a) of the PHS Act (draft, 2014)
8. Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (draft, 2015)
9. Labeling for Biosimilar Products (draft, 2016)
10. Considerations in Demonstrating Interchangeability With a Reference Product (draft, 2017)

http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm290967.htm

Key Concept #1: Goals of "Stand-alone" and Biosimilar Development are Different

"Stand-alone" Development Program, 351(a)
Goal: To establish safety and efficacy of a new product

"Abbreviated" Development Program, 351(k)
Goal: To demonstrate biosimilarity (or interchangeability) to a reference product

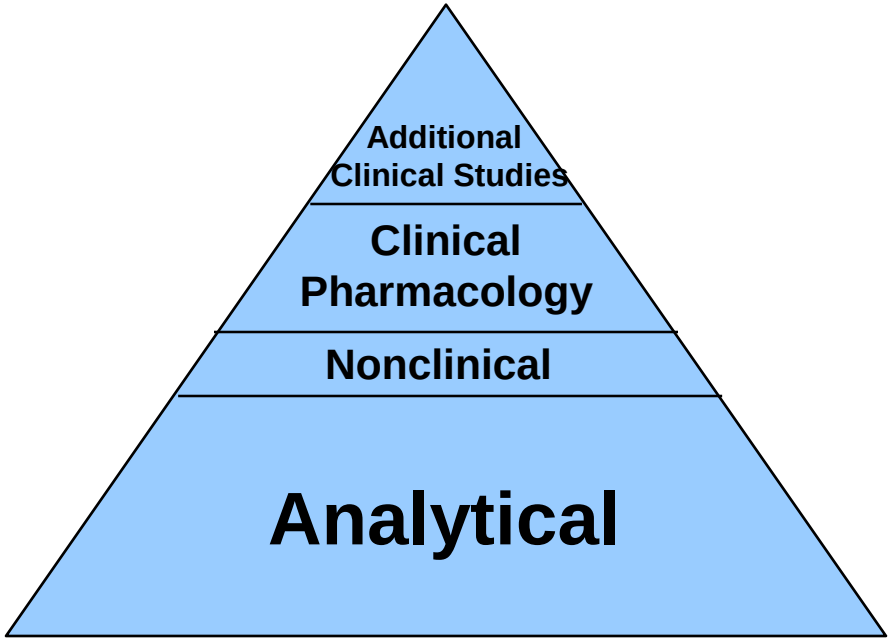


What does this difference mean from a development perspective?

Key Concept #2:
Stepwise Evidence Development

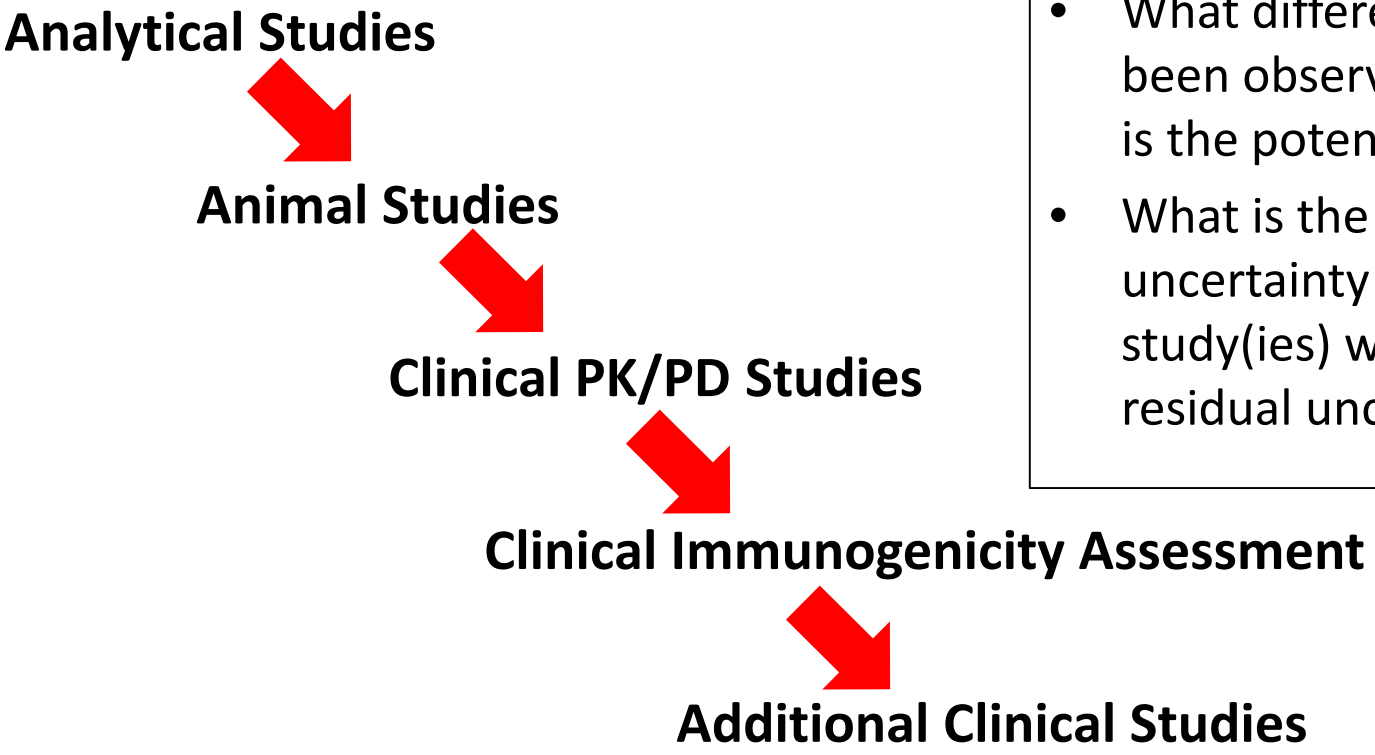
- FDA has outlined a **stepwise approach** to generate data in support of a demonstration of biosimilarity
- Evaluation of residual uncertainty at each step of data generation
- *Totality-of-the-evidence* approach in evaluating biosimilarity

- **There is no one "pivotal" study that demonstrates biosimilarity**



No "one size fits all" assessment

- Apply a step-wise approach to data generation and the evaluation of residual uncertainty*

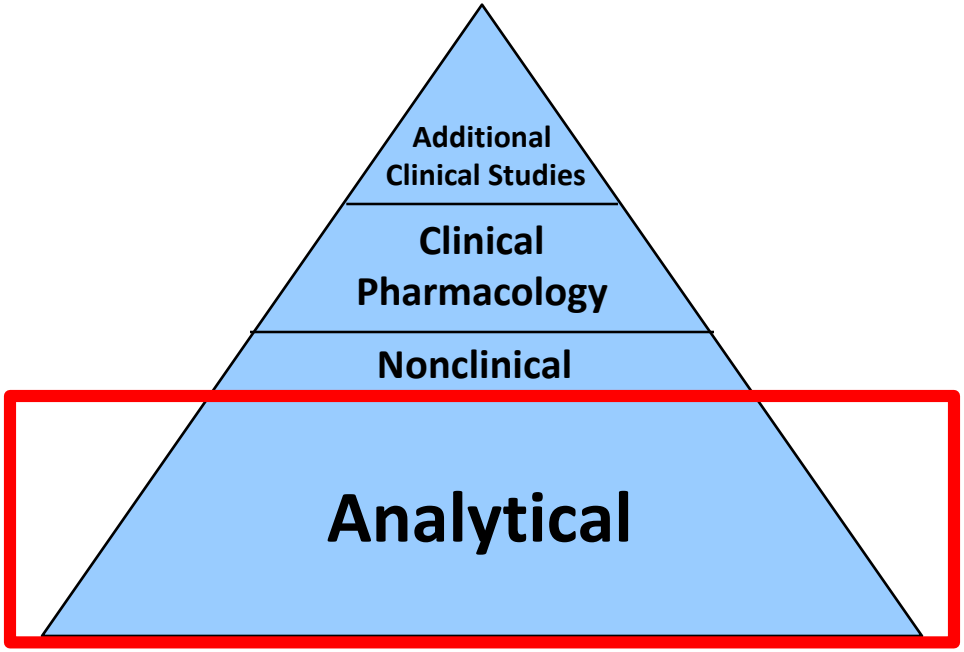


- What differences have been observed and what is the potential impact?
- What is the residual uncertainty and what study(ies) will address the residual uncertainty?

* The list is not intended to imply that all types of data described here are necessary for any given biosimilar development program. FDA may determine, in its discretion, that certain studies are unnecessary in a 351(k) application.

Key Concept #3:
Analytical Similarity Data -
The Foundation of a Biosimilar Development Program

- Extensive **structural and functional characterization**



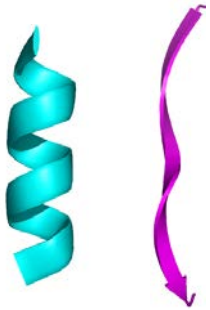
"Abbreviated" Development Program, 351(k) BLA

Hierarchy of protein structure

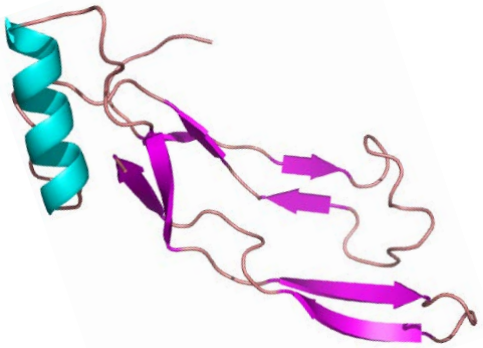
Primary

Asp
His
Ala
Iso
Val
Gln
Tyr
Leu

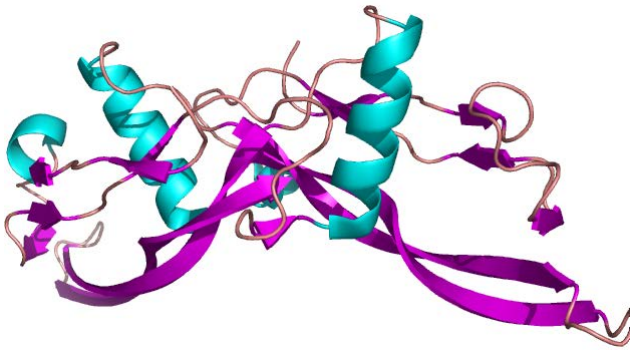
Secondary



Tertiary



Quaternary



- Protein Heterogeneity
- Lot-to-lot variability
- All need to be evaluated as part of analytical similarity studies

Assessing Analytical Similarity

- Comprehensive structural and functional analyses
- Comparative assessment of attributes including:
  - Amino acid sequence and modifications
  - Folding
  - Subunit interactions
  - Heterogeneity (size, aggregates, charge, hydrophobicity)
  - Glycosylation
  - Bioactivity
  - Impurities
- If a molecule is known to have multiple biological activities, where feasible, each should be demonstrated to be highly similar between the proposed biosimilar product and the reference product
- **Understand** the molecule and function and identify **critical quality attributes**

Generating Analytical Similarity Data

- Characterize reference product quality characteristics and product variability
- Manufacturing process for the proposed biosimilar product should be designed to produce a product with minimal or no difference in product quality characteristics compared to the reference product
- Identify and evaluate the potential impact of differences observed and what study(ies) will address the residual uncertainty
- **Understanding the relationship** between quality attributes and the clinical safety & efficacy profile aids ability to determine **residual uncertainty** about biosimilarity and to predict expected "clinical similarity" from the quality data.

Statistical Analysis of Analytical Similarity Data

- Statistical analyses of the analytical similarity data are conducted to support a demonstration that the proposed biosimilar product is highly similar to the reference product

- Quality attributes are ranking based on criticality with regard to their potential impact on activity, PK/PD, safety, immunogenicity, and other factors

- Data are then analyzed by various testing methodologies

Animal Data

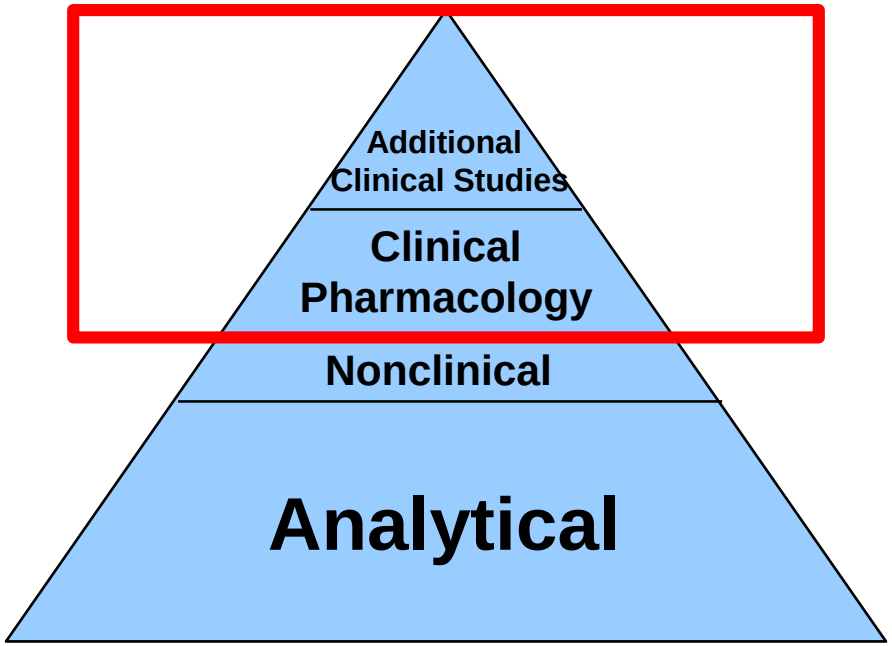
- Animal toxicity data are useful when uncertainties remain about the safety of the proposed product prior to initiating clinical studies

- The scope and extent of animal studies, including toxicity studies, will depend on publicly available information and/or data submitted in the biosimilar application regarding the reference product and the proposed biosimilar product, and the extent of known similarities or differences between the two

- A comparison of PK/PD in an animal model may be useful

Key Concept # 4:
Role of Clinical Studies

- The nature and scope of clinical studies will depend on the extent of residual uncertainty about the biosimilarity of the two products **after** conducting structural and functional characterization and, where relevant, animal studies.



"Abbreviated" Development Program, 351(k) BLA

Type of Clinical Data

- As a scientific matter, FDA expects an adequate clinical PK, and PD if relevant, comparison between the proposed biosimilar product and the reference product.

- As a scientific matter, at least 1 clinical study that includes a comparison of the immunogenicity of the proposed and reference product generally will be expected.

- As a scientific matter, a comparative clinical study will be necessary to support a demonstration of biosimilarity if there are **residual uncertainties** about whether there are clinically meaningful differences between the proposed and reference products based on structural and functional characterization, animal testing, human PK and PD data, and clinical immunogenicity assessment.

Comparative Human PK and PD Data

- PK and/or PD is generally considered the most sensitive clinical study/assay in which to assess for differences between products, should they exist

- PK
  - Demonstrate PK **similarity** in an adequately sensitive population to detect any differences, should they exist
- PD
  - **Similar** PD using PD measure(s) that reflects the mechanism of action (MOA) or reflects the biological effect(s) of the drug

- **PK and PD similarity** data supports a demonstration of biosimilarity with the assumption that similar exposure (and pharmacodynamic response, if applicable) will provide **similar efficacy and safety** (i.e., an exposure-response relationship exists)

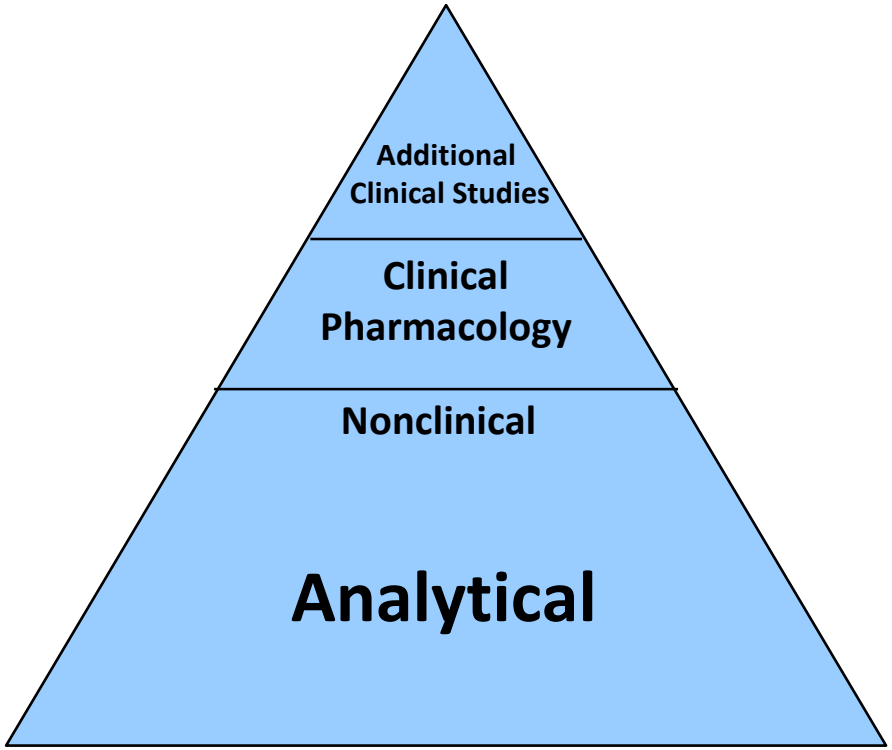
Comparative Clinical Study

- A comparative clinical study for a biosimilar development program should be designed to investigate whether there are clinically meaningful differences in safety and efficacy between the proposed product and the reference product.
- Population, endpoint, sample size and study duration should be adequately sensitive to detect differences, should they exist.
- Typically, an equivalence design would be used, but other designs may be justified depending on product-specific and program-specific considerations.
- Assessment of safety and immunogenicity

Key Concept # 5: Extrapolation

- The potential exists for a biosimilar product to be approved for one or more conditions of use for which the reference product is licensed based on extrapolation
- Sufficient scientific justification for extrapolation is necessary
- Differences between conditions of use (e.g., indications) do not necessarily preclude extrapolation
- Extrapolation from information in 351(k) BLA and FDA's finding for the reference product to other indications previously approved for the reference product, considering for each indication:
  - MoA in each condition of use
  - PK and biodistribution in different patient populations
  - Immunogenicity in different patient populations
  - Differences in expected toxicities in each condition of use and patient population

Totality of Evidence



"Abbreviated" Development Program, 351(k) BLA

- FDA will consider the totality of the data and information submitted in the application...
- FDA intends to use a risk-based approach to evaluate all available data and information submitted

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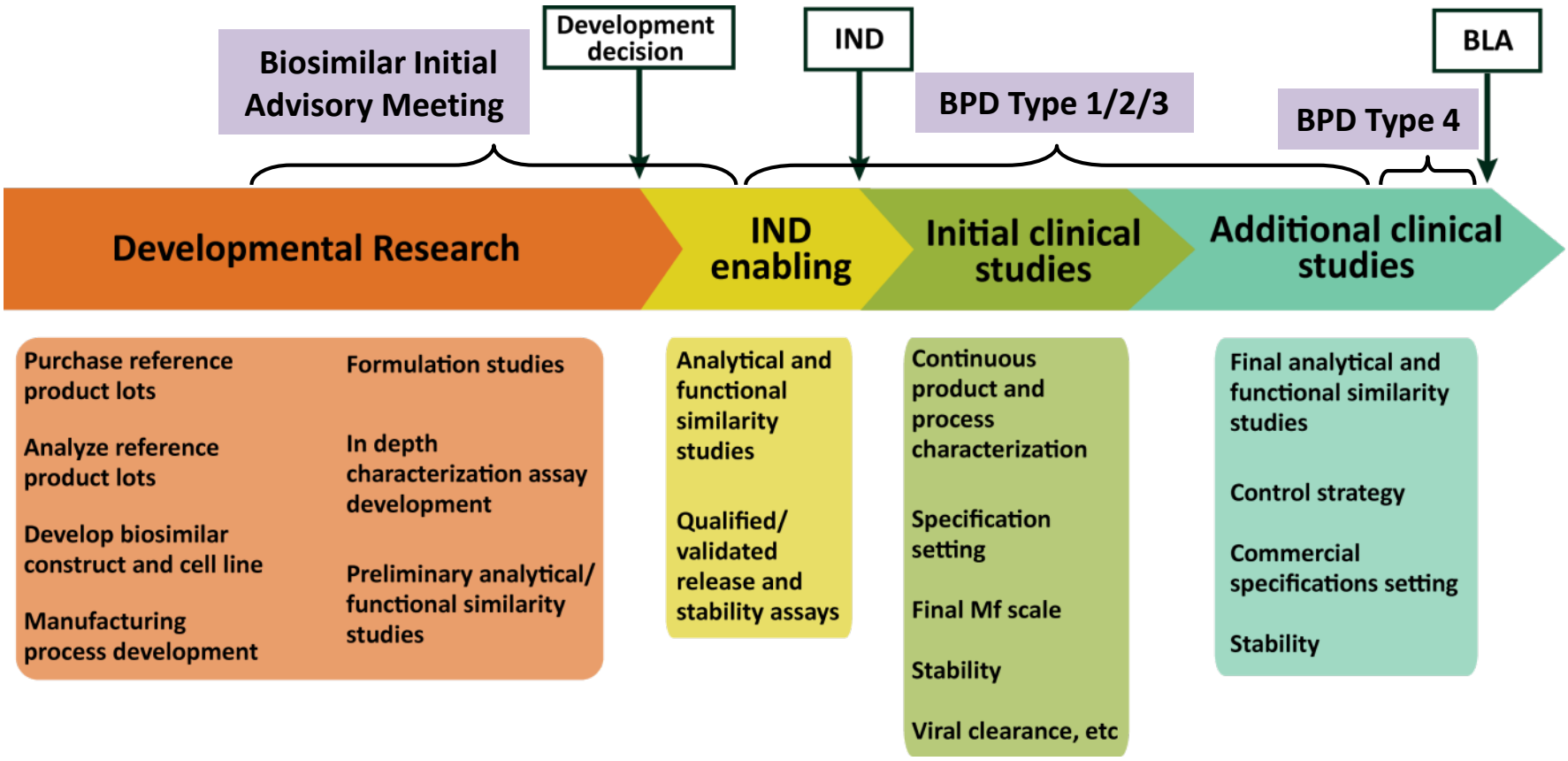
CMC Development of Biosimilars

Biosimilar Products - A Frontloaded Product Quality Development



➢ *Compressed CMC development program*

Adapted from "Quality Considerations for Biosimilars" by Marjorie Shapiro. DIA/FDA Biosimilars Conference. Sep, 2012

Invest in Acquiring Process and Product Knowledge Early in Development

- A 351(k) BLA must meet CMC regulatory expectations as any 351(a) BLA
- A biosimilar is not just a copy of a reference product.
  - CQAs are more than the listed attributes in a CoA
- Process and product knowledge are important for developing an adequate control strategy and product lifecycle management strategies
- Can use publicly available information
  - Sponsors should justify relevance of data to the particular product

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Clarification on CMC Expectations for Biosimilar BLAs

Complete Application

- Ensure a well-organized, complete application:
  - Provide the data and supporting information in the appropriate section (ICH M4Q)
  - Provide narrative describing relevance of data, reports
    - Generic reports
  - Use eCTD format, working hyperlinks, English translations, etc.
- This will:
  - Help ensure an application is fileable
  - Make the review process more efficient
  - Reduce the number of information requests
  - Reduce submission of major amendments

Pre-License Inspection (PLI)

- Critical aspect of application review
- PLI is the same for the 351k:
  - All facilities should be ready for inspection at the time of submission (form FDA 356h) – Filing requirement.
  - The product should be manufactured during the inspection to allow for a meaningful inspection (21 CFR 600.21)
  - Production schedule for all locations should be available at time of BLA submission.
- Scope: Traditional PLI topics as well as similarity data
  - Provide in the 3.2.R, Regional section, a listing of all sites where the analytical similarity assessment was conducted and identify the testing site(s) for each method.
  - In instances that similarity site is non a registered GMP facility, a “site visit” may be arranged.

Process and Analytical Method Validation

- A 351 (k) BLA should include process validation data supporting commercial manufacture of drug substance and drug product at all the proposed manufacturing sites.
  - Process characterization studies can be use to support certain conditions
  - Bracketing approach may be used
    - Recommend discussion with the Agency.
- Provide method validation and when appropriate, method transfer data to support all testing facilities.
  - Develop and validate analytical methods early in development

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Stability Data

- Provide stability data on at least three batches of final container product representative of that which will be used at manufacturing scale.

- At minimum, 6 months of data should be submitted at the time of submission (storage periods >6 months).

- Product expiration dating is based upon the actual real time stability data submitted in support of the application.
  - May provide stability updates

- Refer to ICHQ5C for additional information

Information Requests

- Address the request with data and justification
- Request clarification when needed
- Respond in a timely manner
  - Prevent submission of a major amendment late in the review cycle

Summary

- Development of a biosimilar product is different from "stand-alone" product development, however,
  - CMC regulatory expectations are the same for 351(k) and 351(a) BLAs

- Invest in acquiring process and product knowledge early in development.
  - Process and product knowledge are important for developing an adequate control strategy and product lifecycle management strategies

Summary

- BPD meetings may be used to request advice not only on biosimilarity issues but also on process development.

Biosimilar Update

- **As of September 1, 2017,** 69 programs were enrolled in the Biosimilar Product Development (BPD) Program. CDER has received meeting requests to discuss the development of biosimilars for 26 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 September 1, 2017, 9 companies have publicly announced submission of 16 351(k) BLAs to FDA.
- Six 351(k) BLAs for biosimilar products have been approved.
  - Zarxio (filgrastim-sndz)
  - Inflectra (infliximab-dyyb)
  - Erelzi (etanercept-szzs)
  - Amjetiva (adalimumab-atto)
  - Renflexis (infliximab-abda)
  - Cyltezo (adalimumab-adbm)

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Acknowledgements

- Leah Christl
- Emanuela Lacana
- Susan Kirshner

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Thank you for your attention.

Questions?