Overview of the Regulatory Framework and FDA's Guidance for the Development and Approval of Biosimilar and Interchangeable Products in the US

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Overview of Presentation

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  - Background
  - Terminology
  - General Requirements
- Development of Biosimilars
  - Status in the U.S.
  - Specific Development Concepts
- Overview of Demonstrating Interchangeability
- Using biosimilar and interchangeable products

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**.**

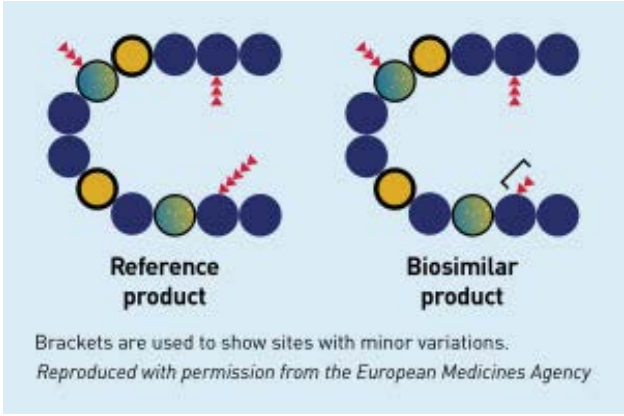
What is Meant by Abbreviated Licensure Pathway?

- 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.
- Once a biosimilar or interchangeable has been approved by FDA, patients and health care providers will be able to rely upon the safety and effectiveness of an FDA-approved biosimilar or interchangeable product just as they would for the reference product that the biosimilar was compared to.

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.

– An application submitted under section 351(a) of the PHS Act is a "stand-alone" application that must contain all information and data necessary to demonstrate that the proposed product is safe, pure and potent.

– In contrast, an application submitted under section 351(k) needs to demonstrate that the proposed product is biosimilar to the reference product. For licensure, a proposed biosimilar relies on (among other things) comparative data with the reference product, as well as publicly-available information regarding FDA's previous determination that the reference product is safe, pure and potent.

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.

Challenge Question #1

A biosimilar product is?

A: Highly similar to a reference product

B: Different from a reference a product in a clinically meaningful way

C: Both A & B

D: None of the above

Challenge Question #2

What is meant by an abbreviated licensure pathway for biosimilar and interchangeable products?

A: The company has less paperwork to complete

B: FDA has less time to review the application

C: 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.

D: None of the above

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Development of Biosimilars in the U.S.

Biosimilars Program

- As of December 1, 2017, 60 programs were enrolled in the Biosimilar Product Development (BPD) Program. CDER has received meeting requests to discuss the development of biosimilars for 27 different reference products.

- Since program inception and as of December 1, 2017, 11 companies have publicly announced submission of 20 351(k) BLAs to FDA.

- As of December 1, 2017, eight 351(k) BLAs for biosimilar products have been approved.
  - Zarxio (filgrastim-sndz)
  - Erelzi (etanercept-szzs)
  - Renflexis (infliximab-abda)
  - Mvasi (bevacizumab-awwb)
  - Inflectra (infliximab-dyyb)
  - Amjetiva (adalimumab-atto)
  - Cyltezo (adalimumab-adbm)
  - Ogivri (trastuzumab-dkst)

FDA Biosimilars 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. Biosimilars: Additional Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009 (draft, 2015)
8. Labeling for Biosimilar Products (draft, 2016)
9. Considerations in Demonstrating Interchangeability With a Reference Product (draft, 2017)
10. Statistical Approaches to Evaluate Analytical Similarity (draft, 2017)

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

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Overview of FDA's Approach to the Development of Biosimilars

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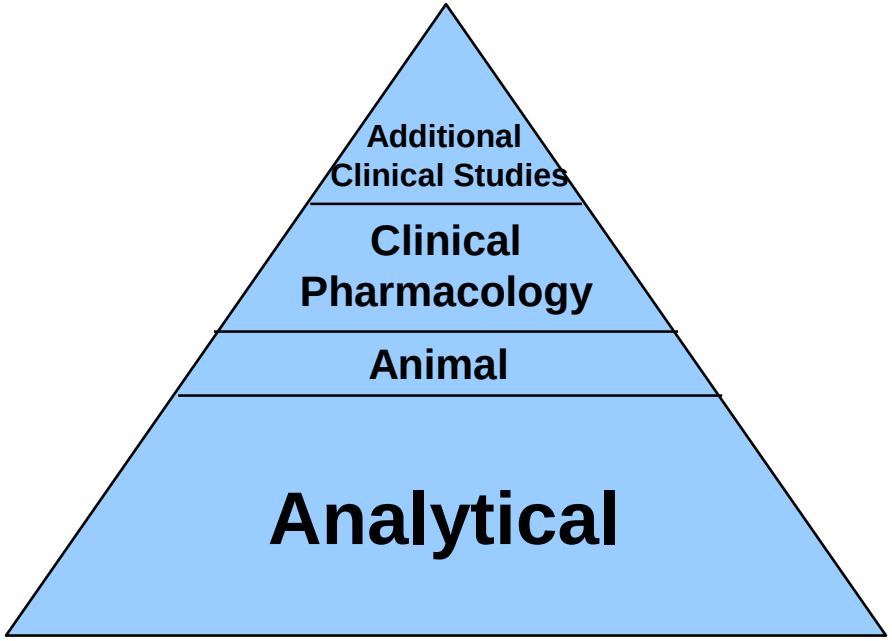
Key Development Concepts

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

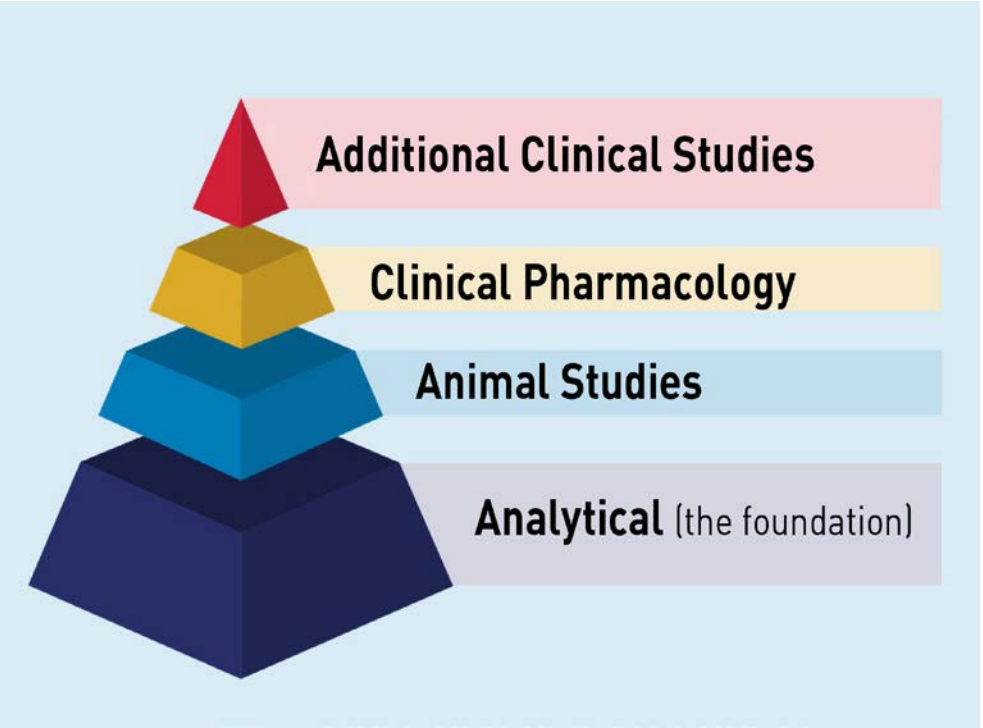


What does this difference mean from a development perspective?

Key Concept #2: Stepwise Evidence Development

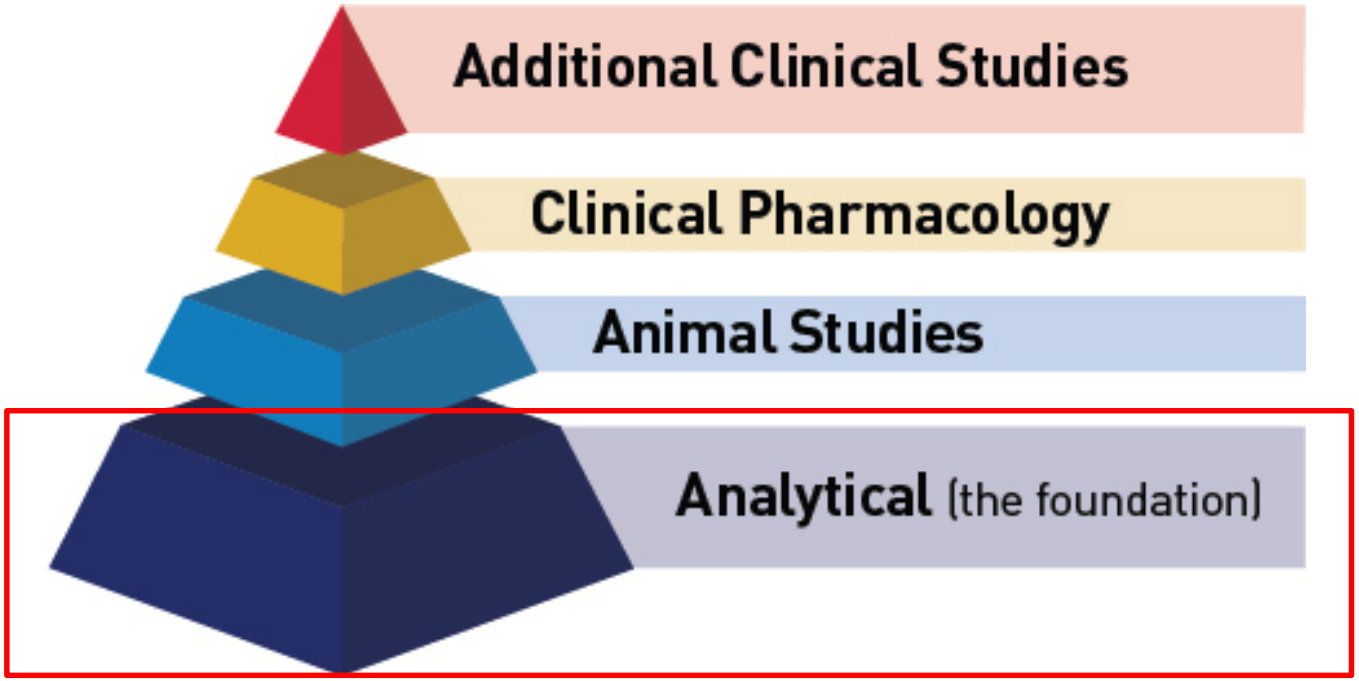
- FDA has outlined a **stepwise approach** to generate data in support of a demonstration of biosimilarity
- Evaluation of residual uncertainty at each step of data generation
- *Totality-of-the-evidence* approach in evaluating biosimilarity – no "one-size fits all" assessment

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

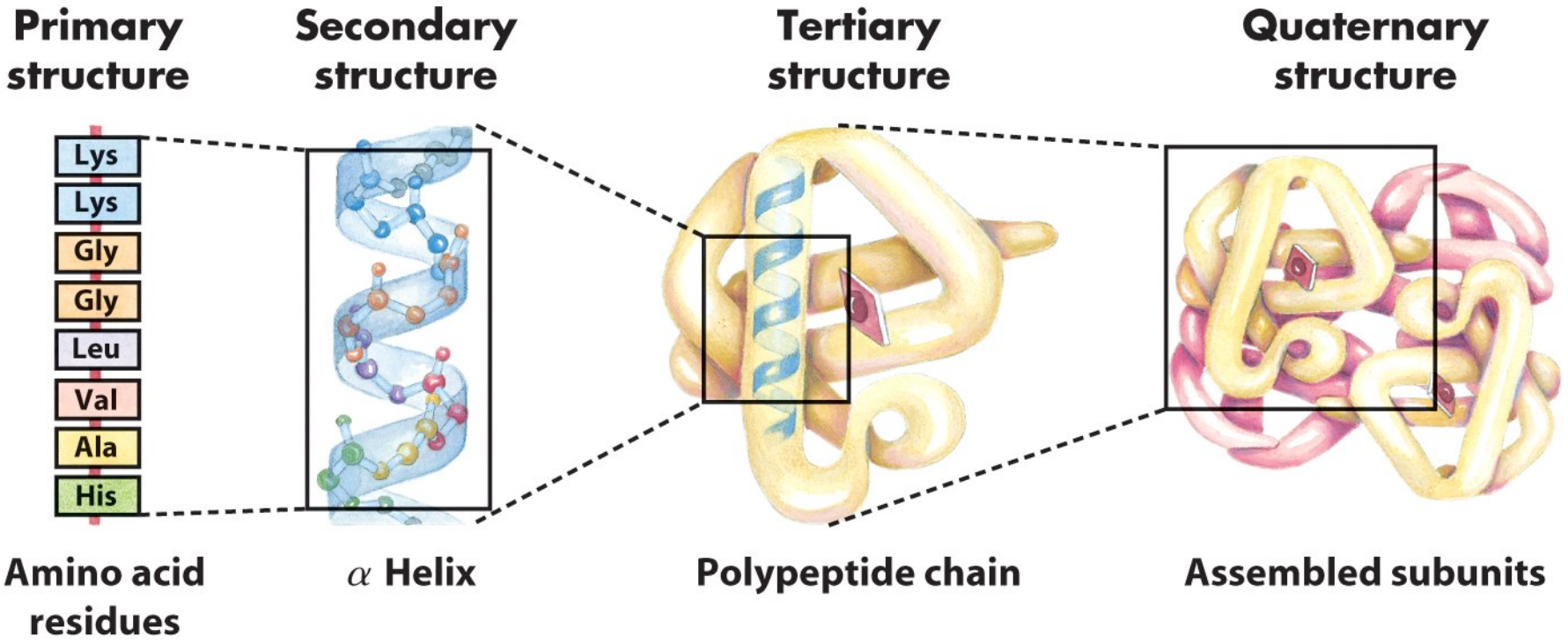


Key Concept #3: Analytical Similarity Data - The Foundation of a Biosimilar Development Program

- Extensive **structural and functional characterization**



Hierarchy of protein structure



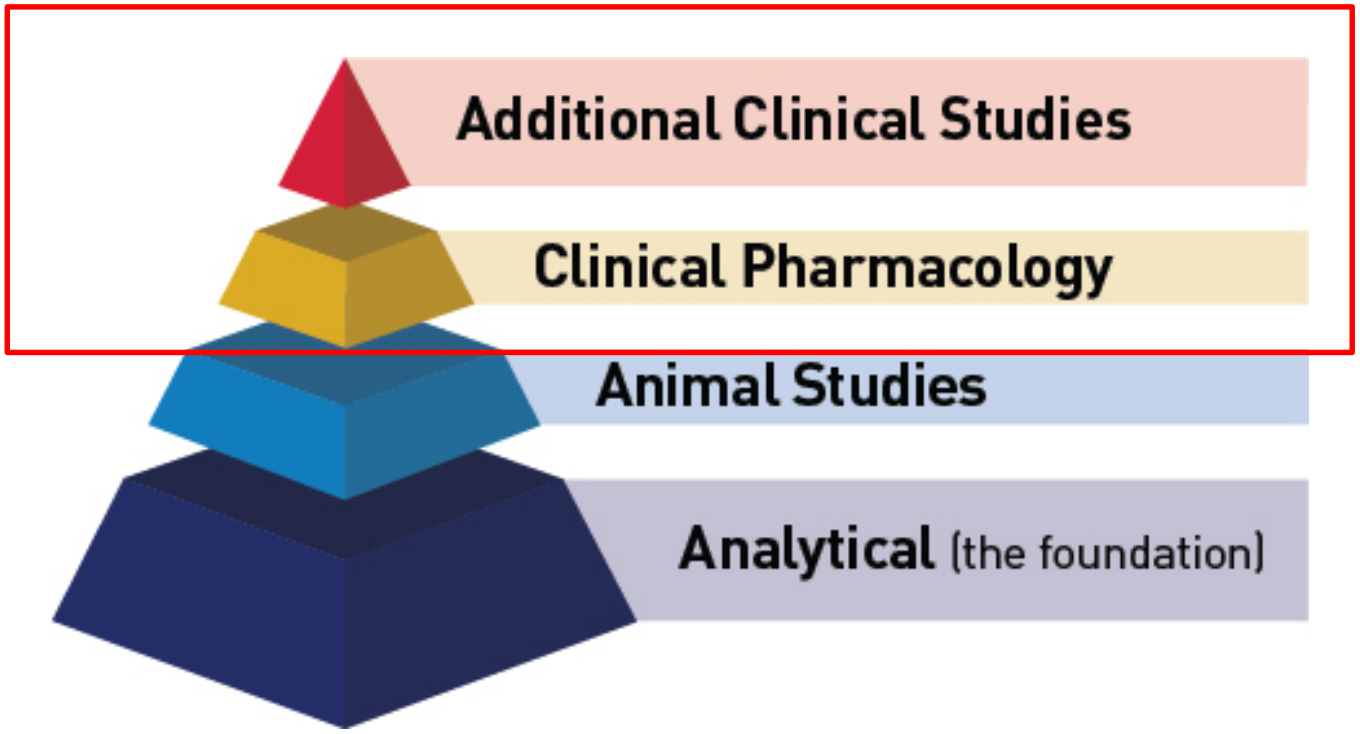
- **Protein Heterogeneity**
- **Lot-to-lot variability**
- **All need to be evaluated as part of analytical similarity studies**

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.

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.



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)

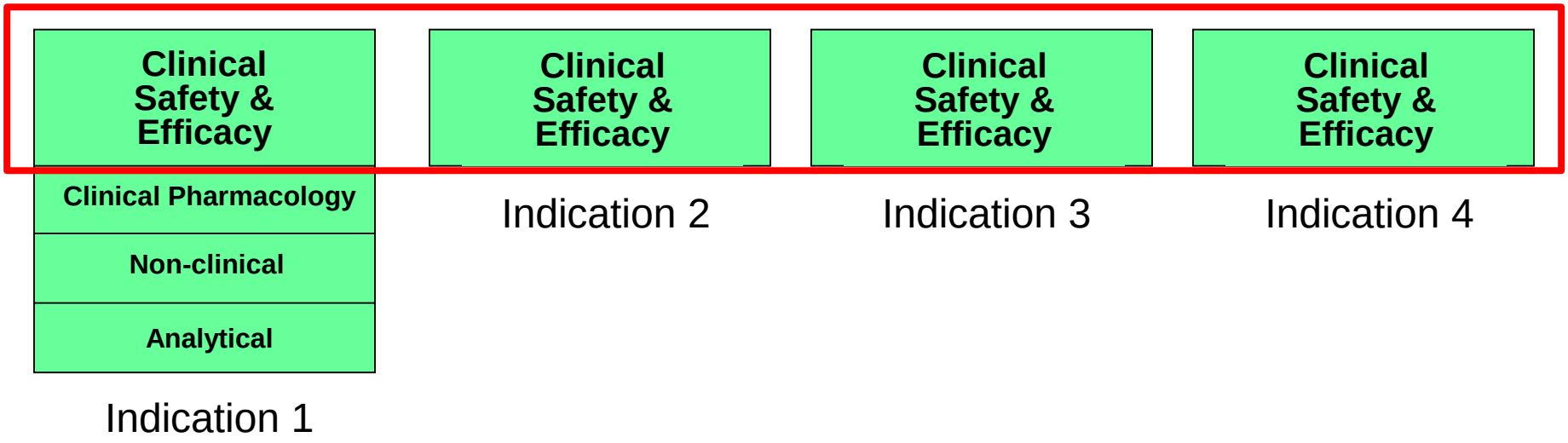
Comparative Clinical Study

- 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

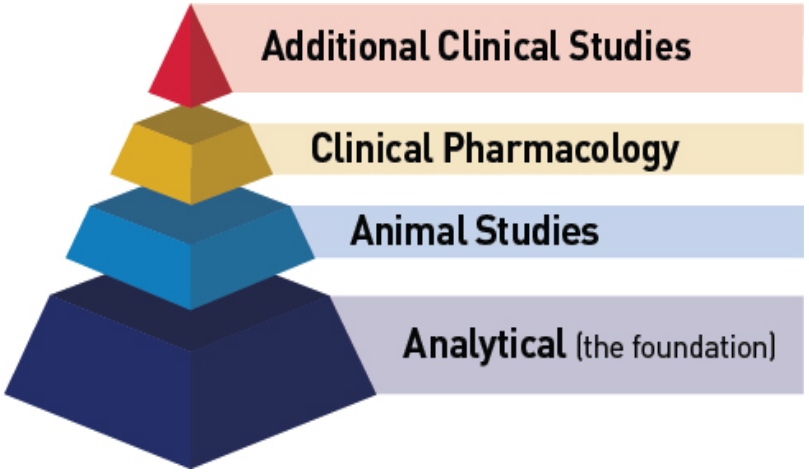
- The potential exists for a biosimilar product to be approved for one or more conditions of use for which the reference product is licensed based on extrapolation
- Sufficient scientific justification for extrapolation is necessary
- Differences between conditions of use (e.g., indications) do not necessarily preclude extrapolation
- FDA guidance outlines factors to consider, including:
  - 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

Extrapolation Considerations: "Stand-alone" Drug Development



Extrapolation Considerations: "Stand-alone" vs. Biosimilar Development

Clinical Safety & Efficacy	Clinical Safety & Efficacy	Clinical Safety & Efficacy	Clinical Safety & Efficacy
Clinical Pharmacology	Indication 2	Indication 3	Indication 4
Non-clinical			
Analytical			



The concept of extrapolation is based on:

- All available data and information in the biosimilar application
- FDA's previous finding of safety and efficacy for other approved indications for the reference product
- Knowledge and consideration of various scientific factors for each indication

Biosimilar extrapolation is based on all available data in the 351(k) BLA and FDA's finding for the reference product, not from the indication(s) studied for the biosimilar to other non-studied indications

Challenge Question #3

What is the purpose of a biosimilar development program, versus a "standalone" development program?

A: to demonstrate safety and efficacy

B: to demonstrate the biosimilar product is highly similar to the reference product

C: to demonstrate that there are no clinically meaningful differences

D: Both B and C

Challenge Question #4

What is the foundation of the biosimilar development program?

A: Analytical

B: Nonclinical

C: Clinical pharmacology

D: Additional Clinical Studies

Challenge Question #5

What is the purpose of clinical studies in a biosimilar development program?

A: To detect differences in exposure and response between the proposed product and the reference product

B: To independently demonstrate the safety and effectiveness of the proposed product

C: To investigate whether there are clinically meaningful differences in safety and efficacy between the proposed product and the reference product

D: Both A and C

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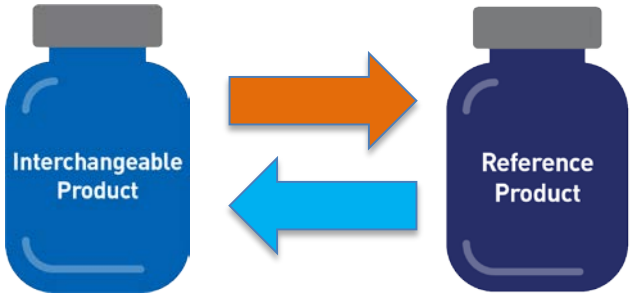
Considerations in Demonstrating Interchangeability With a Reference Product



Draft Guidance for Industry

Interchangeability

Interchangeable or **Interchangeability:**

- the biological product is **biosimilar** to the reference product;
- it **can be expected** to produce the **same clinical result** as the reference product **in any given patient**; and
- for a product that is administered more than once to an individual, the risk in terms of **safety or diminished efficacy of alternating or switching** between use of the product and its reference product is not greater than the risk of using the reference product without such alternation or switch.

An interchangeable product **may be substituted** for the reference product without the intervention of the health care provider who prescribed the reference product.

General Principles

- When a product is first licensed as a **biosimilar**, that licensure may be referenced to support a showing for this statutory criterion for demonstrating interchangeability

- FDA expects that sponsors will submit data and information to support a showing that that the proposed interchangeable product **can be expected** to produce the same clinical result as the reference product in ***all*** of the reference product's licensed conditions of use
  - The data and information may vary depending on the nature of the proposed interchangeable product.
  - The data and information should include a scientific justification as to why **any differences** that exist between the reference product and the proposed interchangeable product, with respect to the factors described in the guidance, **do not preclude a showing** that the proposed interchangeable product **can be expected** to produce the same clinical result as the reference product in any given patient.

General Principles Con't

- FDA expects that applications for a product administered more than once to an individual generally will include data from a **switching study or studies** in one or more appropriate conditions of use

- Sponsors should evaluate the proposed product's **presentation**, including product design and user interface, relative to the reference product

Additional Data and Information Needed to Support a Demonstration of Interchangeability

Switching Study to demonstrate that **the risk in terms of safety or diminished efficacy of alternating or switching** between use of the proposed interchangeable product and the reference product is not greater than the risk of using the reference product without such alternation or switch.

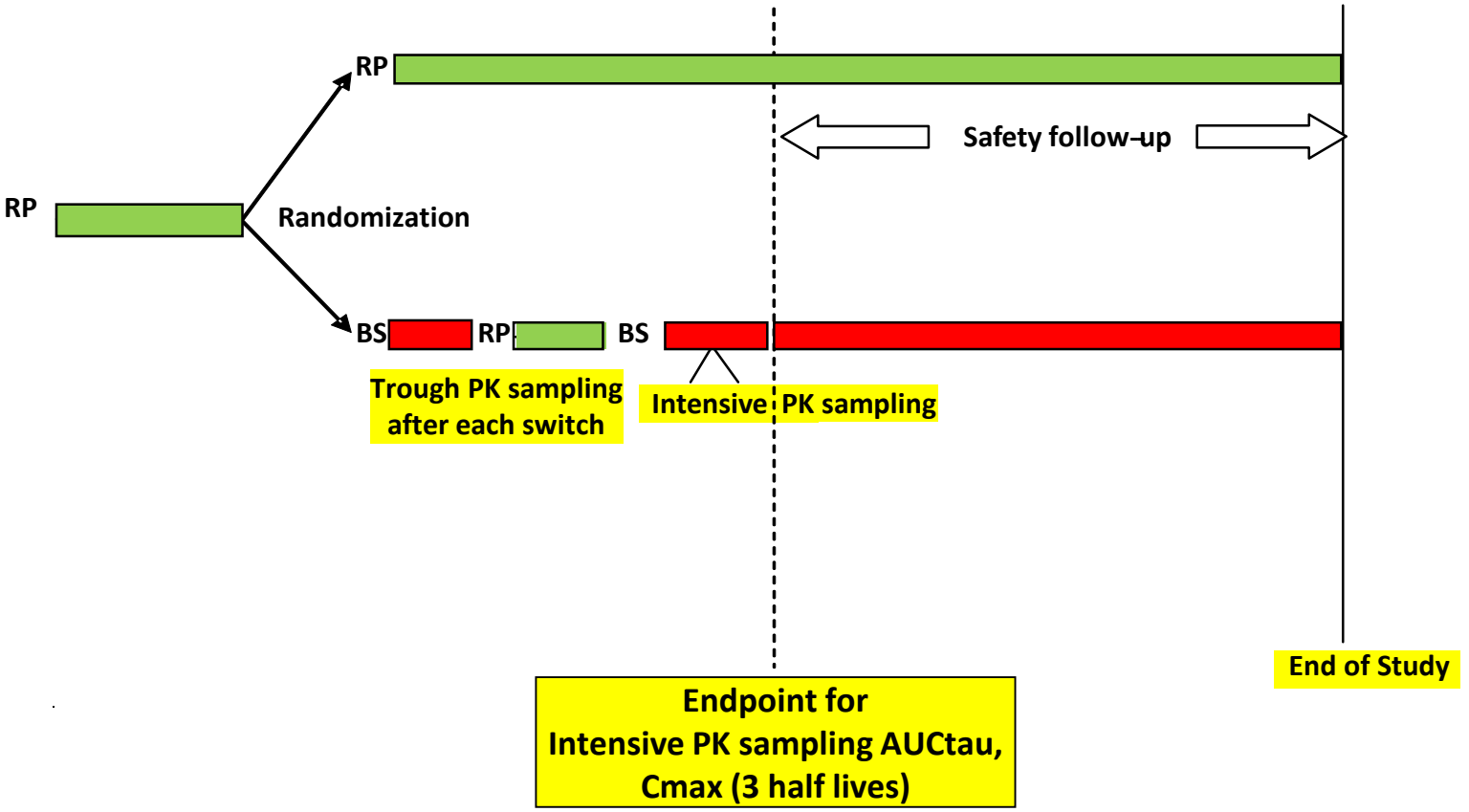
Design of a Switching Study

Considerations will be product-specific and should generally consider the scenario of switching where there is the **most clinical concern for patients**. Sponsors should consider:

- **Study Endpoints**- primary endpoint should assess the impact of switching on **clinical PK, and PD** if available as these endpoints are generally most likely to be sensitive to changes in immunogenicity and/or exposure that may arise as a result of alternating or switching; **immunogenicity and safety** should be descriptively analyzed as secondary endpoints
- **Study Population**- adequately sensitive to allow for detection of differences in PK and PD, common AEs, and immunogenicity
- **Condition of Use to be Studied**- should be one for which the reference product is already licensed and should support extrapolation for other conditions of use
- **Route of Administration**- should study the route that will best assess how a patient's immune response will impact clinical performance

- A switching study should **evaluate changes in treatment that result in two or more alternating exposures (switch intervals)**
- Sufficient scientific justification for **extrapolation** is necessary.

Example of Switching Study Design



Proposed Presentations

- A sponsor developing an interchangeable product generally should not seek licensure for a presentation for which the reference product is not licensed.

- **Differences in the design** of the container closure system or delivery device constituent part between the proposed interchangeable product and the reference product **may be acceptable** provided that
  - the design differences are **analyzed appropriately**, and
  - data are provided to demonstrate that the **changes do not negatively impact the ability of end users, including patient and caregiver end-user groups, to appropriately use these products** when the interchangeable product is substituted for the reference product without the intervention of the prescribing health care provider or additional training before use.

Challenge Question #6

What are the approval criteria for an interchangeable product?

A: the biological product is biosimilar to the reference product

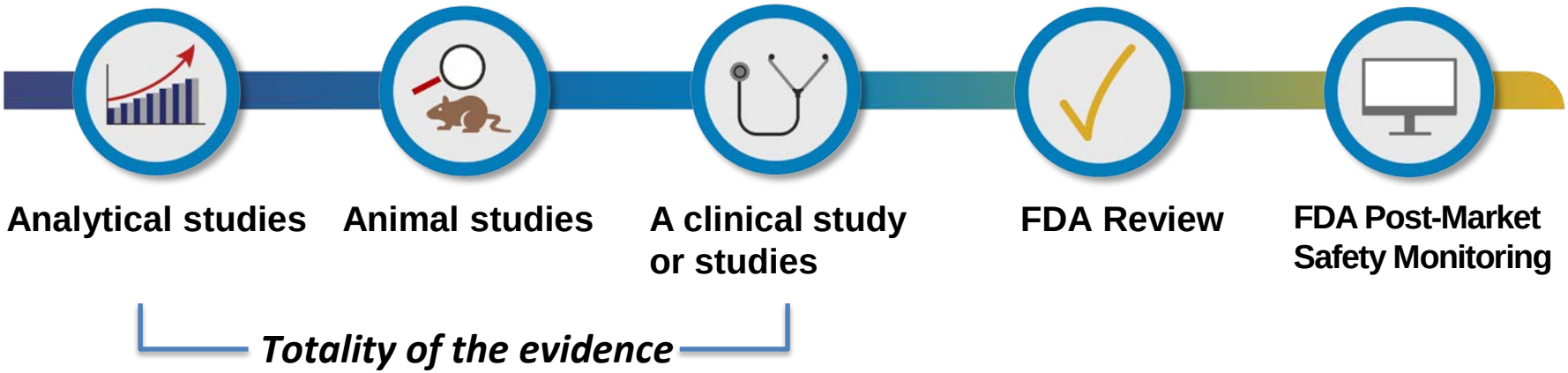
B: it can be expected to produce the same clinical result as the reference product in any given patient

C: for a product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the product and its reference product is not greater than the risk of using the reference product without such alternation or switch.

D: All of the above

Summary

Goal: To establish biosimilarity between proposed product and reference product, not to re-establish safety and effectiveness.



- Approval of a biosimilar or interchangeable product is based on the **integration of various information and the totality of the evidence submitted** by the applicant to provide an overall assessment that the proposed product is biosimilar to or interchangeable with the reference product.

Using Biosimilar and Interchangeable Products

- Patients and their physicians can expect that there will be no clinically meaningful differences between taking a reference product and a biosimilar when these products are used as intended.

- All reference products and biosimilar products meet FDA's rigorous standards for approval for the indications (medical conditions) described in product labeling.

- The FDA's high standard for approval of biosimilar and interchangeable products means that patients and health care professionals **can be confident of the safety and effectiveness of a biosimilar or interchangeable product**, just as they would for the reference product.

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Thank you for your attention.

For more information, go to www.fda.gov/biosimilars

Future webinar: Labeling for biosimilar products; prescribing biosimilar and interchangeable products

Questions?