Biosimilar Biological Products

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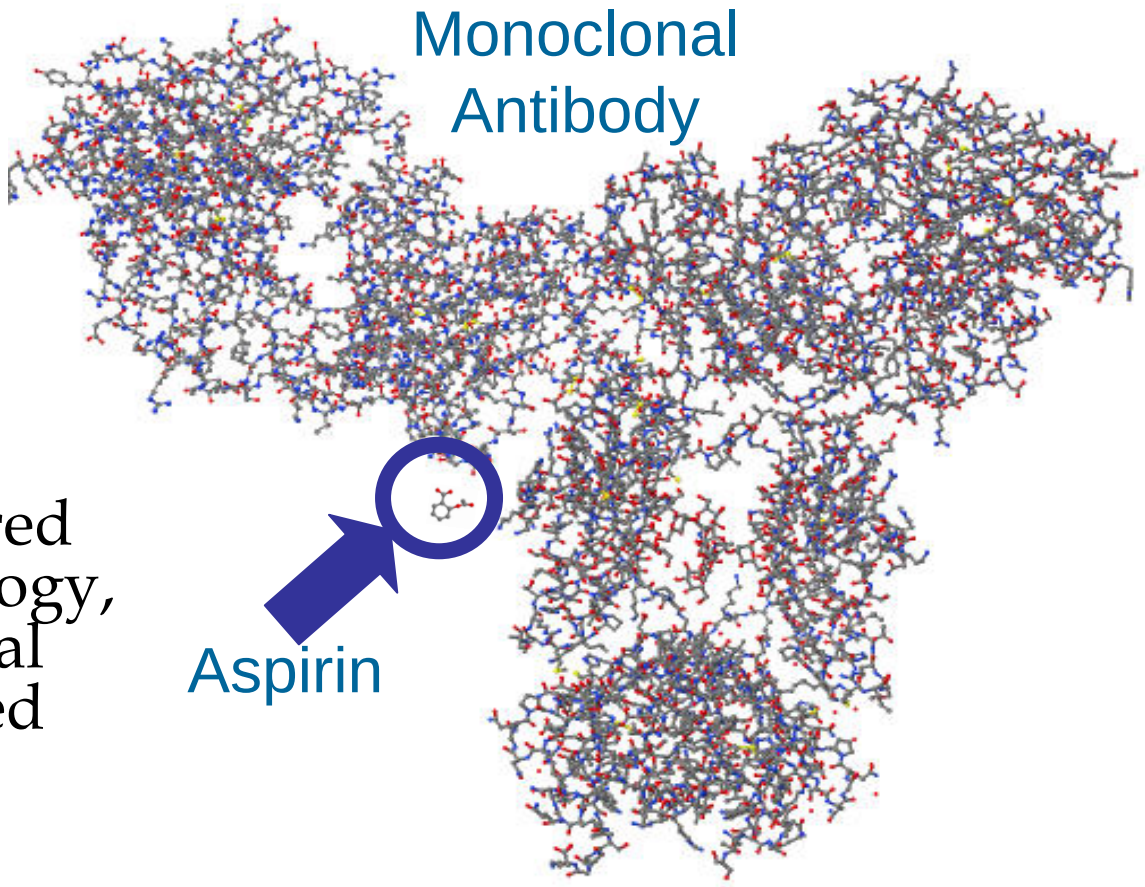
Background

- Public Health Service Act
  - The **Biologics Price Competition and Innovation Act (BPCI Act)** was passed as part of the 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 [section 351(k) of the Public Health Service Act].
- Federal Food Drug and Cosmetic Act (FFDCA)
  - The ***Abbreviated New Drug Application*** process in section 505(j) was established through the 1984 Hatch-Waxman Amendments to the FFDCA thus creating the generic drug program for "small molecule" drugs

Biological Products

- Biological products are **generally** produced using a living system or organism.
- Biological products may be manufactured through biotechnology, derived from natural sources, or produced synthetically.



Overview

- **"Biological Product"** in the Public Health Service Act (PHS Act) now includes "protein":

  . . . a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, ***protein (except any chemically synthesized polypeptide),*** *or analogous product … applicable to the prevention, treatment, or cure of a disease or condition of human beings …*

- Historically, some proteins have been approved as drugs under section 505 of the FD&C Act and other proteins have been licensed as biologics under section 351 of the PHS Act.

- Under the BPCI Act, a protein, except any chemically synthesized polypeptide, will be regulated as a biological product.

BPCI

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 -- only to the extent known for the reference product;
- **Condition(s) of use** proposed in labeling **have been previously approved** for the reference product; and
- Has the **same route of administration**, **dosage form**, and **strength** as the reference product.

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.

General Requirements

A 351(k) application must include information demonstrating biosimilarity based on data derived from:

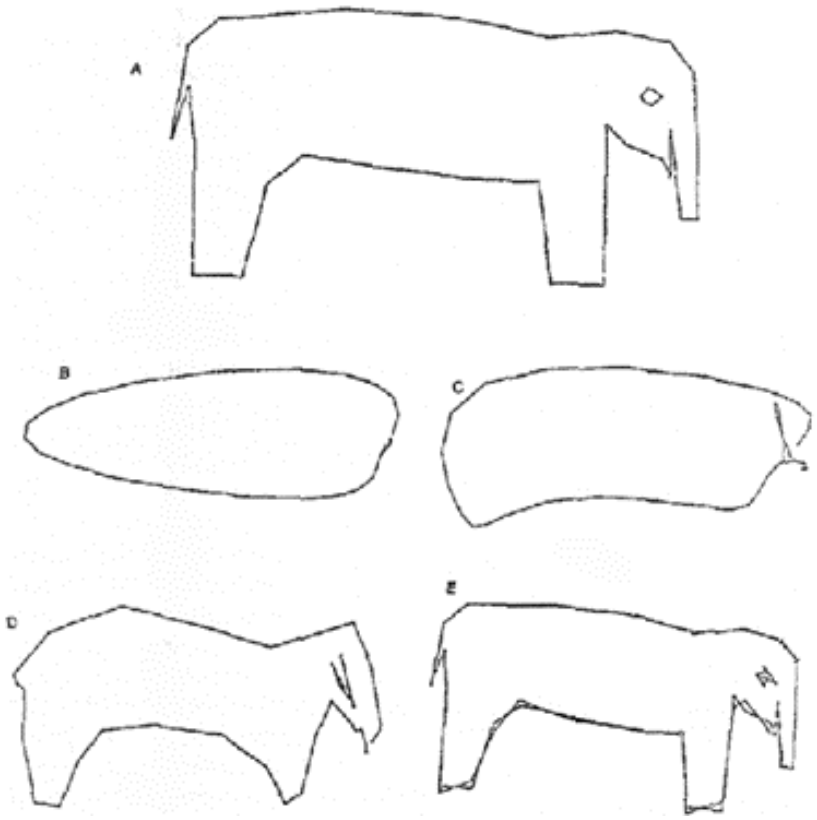
- **Analytical studies** demonstrating that the biological product is "highly similar" to the reference product notwithstanding minor differences in clinically inactive components;
- **Animal studies** (including the assessment of toxicity); and
- A **clinical study or studies** (including the assessment 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.

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

Biosimilarity?

- How close do the proposed biosimilar products (figures B-E) compare to the reference product (figure A)?

- Advances in current state-of-the art analytical methods enhance the likelihood that a product will be highly similar to another product by better targeting the original product's physicochemical and functional properties.

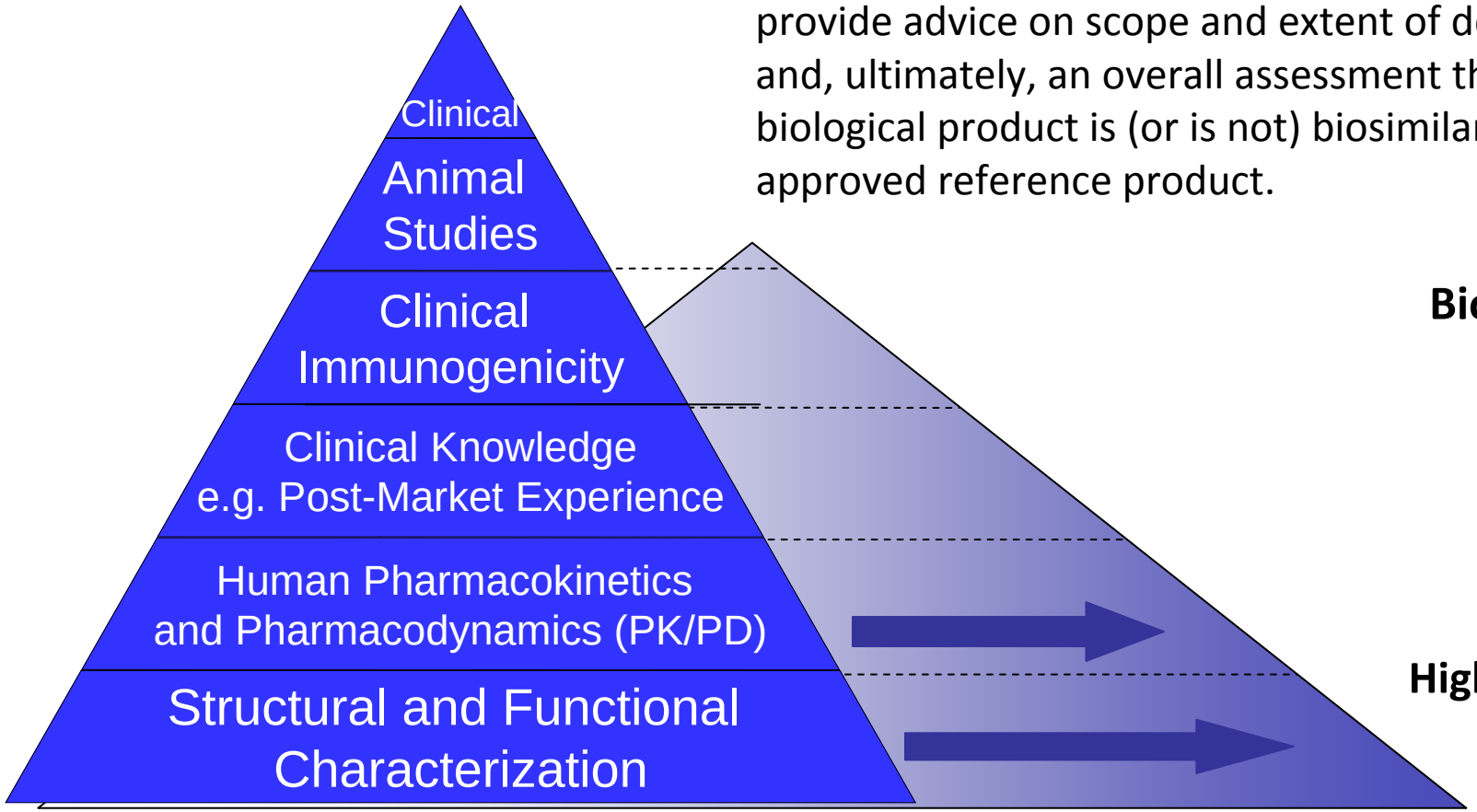


Wel J. "Least squares fitting of an elephant." *Chemtech* Feb. 128-129 (1975).

Totality of the Evidence

No "one size fits all" assessment :

FDA scientists will evaluate the applicant's integration of various types of information to provide advice on scope and extent of develop plan and, ultimately, an overall assessment that a biological product is (or is not) biosimilar to an approved reference product.



Interchangeable or Interchangeability means:

- 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 administered more than once, the **safety and reduced efficacy risks of alternating or switching** are not greater than with repeated use of the reference product without alternating or switching.

Note: The interchangeable product **may be substituted** for the reference product without the authorization of the health care provider.

Status of Biosimilar Sponsor Proposals

- 35 Pre-IND meeting requests for proposed biosimilar products to 11 reference products
- 21 Pre-IND sponsor meetings held to date
- Development programs include:
  - Prospective development programs
    - "Global" programs
  - "Retrospective" development programs
    - Programs seeking licensure in US for similar biological products licensed outside the US
- 9 INDs received

Guidance Development

- Reflects public input and questions received by Agency at regulatory meetings.

- Initial draft guidance targeted to the highest priority issues and directed to clarifying expectations and providing predictability to sponsors initiating biosimilar development programs.

- Initial scope
  - Characterization of the proposed biosimilar product and the reference product (Scientific Considerations; Quality Considerations)
  - Data needed, such as PK/PD, preclinical, clinical (Scientific Considerations; Q&A)
  - Common questions regarding FDA's initial interpretation of certain statutory terms and requirements (Q&A)

Scientific Considerations Draft Guidance

Outlines FDA's *totality-of-the-evidence* approach

- Describes stepwise approach to evidence development, ensuring that development include ***only*** those elements necessary to address residual uncertainty
- Introduces concept that only after a thorough review of data from structural and functional analyses can FDA provide meaningful advice on scope and extent of necessary animal and human testing
- Explains general expectations for human clinical trials
  - At least one study will be expected (immunogenicity/PK-PD)
  - Comparative safety and effectiveness data may be necessary if residual uncertainty exists

Review Paradigm

- FDA traditionally relies on integrating various kinds of evidence in making regulatory decisions; a "totality of the evidence" approach can be applied to assessing biosimilars.

- It is possible to exceed a current state-of-the-art analysis by evaluating more attributes and combination of attributes at greater sensitivities with multiple complementary methods; such fingerprint-like characterization may reduce further the scope and extent of additional animal and clinical studies.

- To provide the best advice on the scope of any required animal and human studies, FDA should already have completed a thorough review of data from structural and functional analyses.

Kozlowski S, et al. Developing the Nation's Biosimilars Program. NEJM 2011 Aug 4;365(5):385-8.

Quality Considerations Draft Guidance

- Focuses on analytical studies that may be relevant to assessing the similarity between a proposed biosimilar protein product and a reference product

- General principles:
  - Importance of extensive analytical, physico-chemical and biological characterization
  - Advances in manufacturing science and Quality by Design approaches may facilitate "fingerprint"-like analysis
  - Identification of lots used in the various analyses for biosimilarity determination

Expanded Scope of a Biological Product

- Protein Definition
  - Any alpha amino polymer with a specific defined sequence that is greater than 40 amino acids in size.

- Chemically synthesized polypeptide definition
  - Any alpha amino acid polymer that (1) is made entirely by chemical synthesis; and (2) is less than 100 amino acids in size

Transition Provisions

- An application for a "biological product" must be submitted under section 351 of the PHS Act.
  - **Exception**: An application for a biological product may be submitted under the FD&C Act through March 23, 2020, if the product is in a product class for which there is already an approved application under the FD&C Act,
    - ***unless*** there is another biological product licensed under section 351(a) of the PHS Act that could serve as its reference product.

- As of March 23, 2020, an application for a biological product approved under section 505 of the FD&C Act will be deemed a biologics license application ("BLA") licensed under section 351 of the PHS Act.

Non-U.S.-Licensed Comparator Products

- The PHS Act defines the "reference product" for a 351(k) application as the "single biological product licensed under section 351(a) against which a biological product is evaluated."

- FDA evaluated public comments to FDA on:
  - whether comparative animal or clinical data with a non-U.S.-licensed product may support a demonstration of biosimilarity to a U.S.-licensed reference product; and
  - if so, what type of bridging data may be required.

"Publicly-Available Information"

- Clarify statutory requirement for submission of "publicly-available information" regarding FDA's previous determination of safety, purity, and potency.

- "Action packages" for approved products available on FDA's Web site.

Exclusivity

- 1st Interchangeable Product
  - The 1st biological product to be licensed as interchangeable is granted a period of exclusivity.
  - During the exclusivity period, a subsequent biological product relying on the same reference product cannot be licensed as interchangeable.
  - Exclusivity calculus is based on date of approval, date of first commercial marketing, and patent litigation milestones.

- Reference Product
  - A 351(k) application may not be submitted until **4 years** after the date of first licensure of the reference product.
  - A 351(k) application may not be approved until **12 years** after the date of first licensure of reference product.

Pediatric Study Requirements

- Under the **Pediatric Research Equity Act** (PREA), all applications for **new active ingredients**, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable (see section 505B of FD&C Act).

- For purposes of PREA, a biological product determined to be:
  - **biosimilar is considered to have a "new active ingredient";**
  - **interchangeable is <u>not</u> considered to have a "new active ingredient."**

- FDA encourages applicants to submit plans for pediatric studies during the IND stage of product development.

EU Biosimilar Products

- EU has approved 14 biosimilars products

- Reference products:
  - Filgrastim
  - Epoetin
  - Somatropin