Biosimilar and Interchangeable Products in the United States: *Scientific and Regulatory Concepts*

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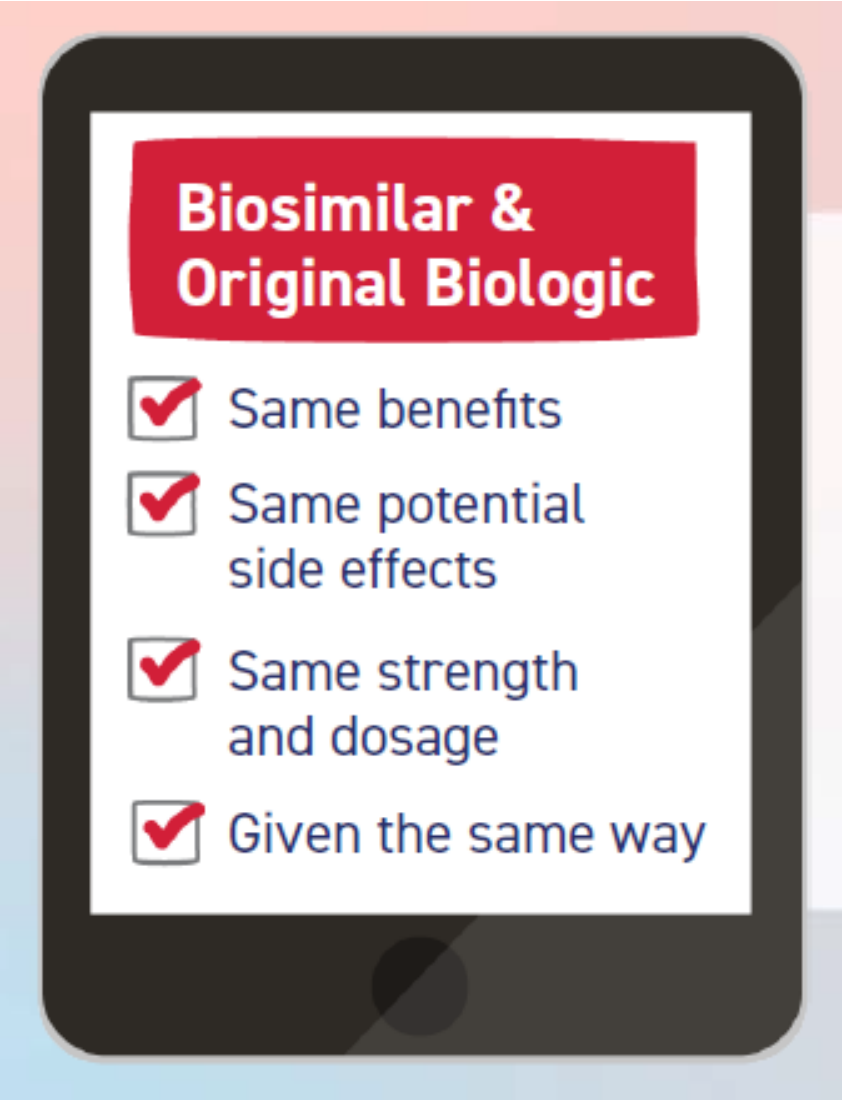
What are Biosimilars?

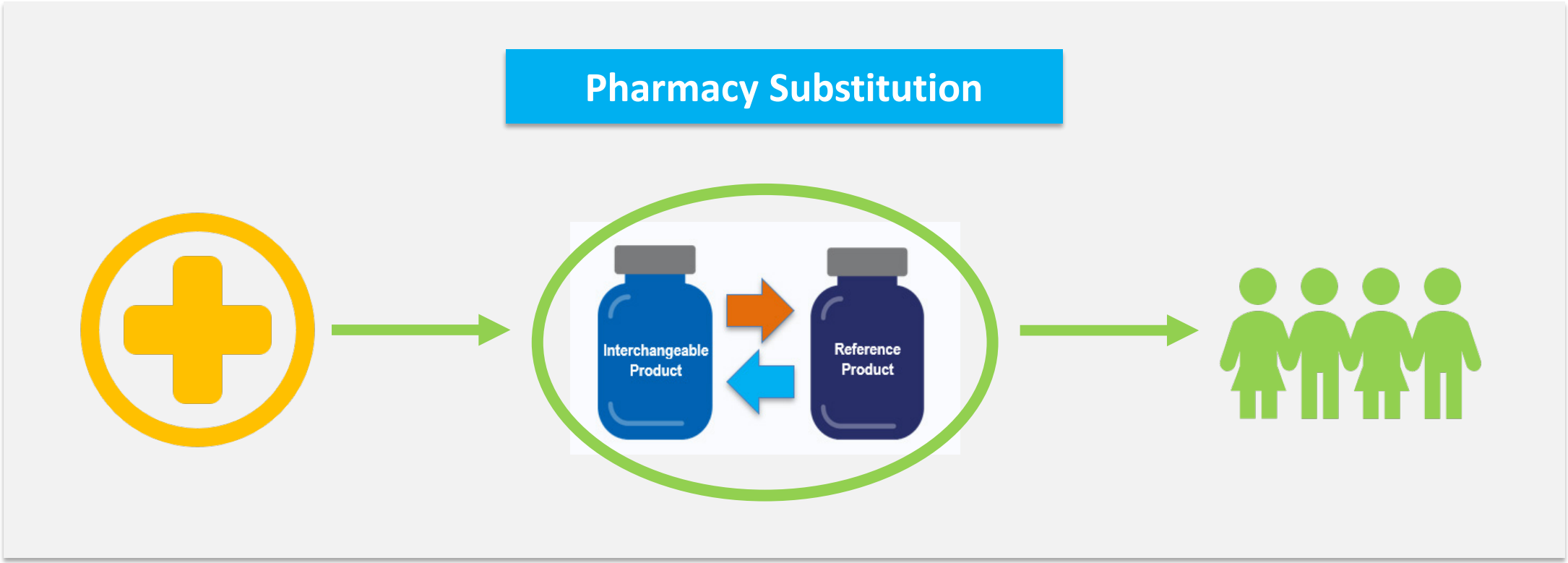


- Biosimilars are FDA-approved, biologic medications that are compared to another medication – the original biologic (also called a reference product)

- Biosimilars are made with the same types of natural sources as the original biologic they were compared to – and ***provide the same treatment benefits***.

What are Interchangeable Biosimilars?

An interchangeable biosimilar product can be ***substituted for the reference product at pharmacies*** without the intervention of the prescribing health care provider.



Regulatory Background

- 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 (safe and effective).

  - The Biologics Price Competition and Innovation Act of 2009 (**BPCI Act**) created an ***abbreviated licensure pathway*** for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product.

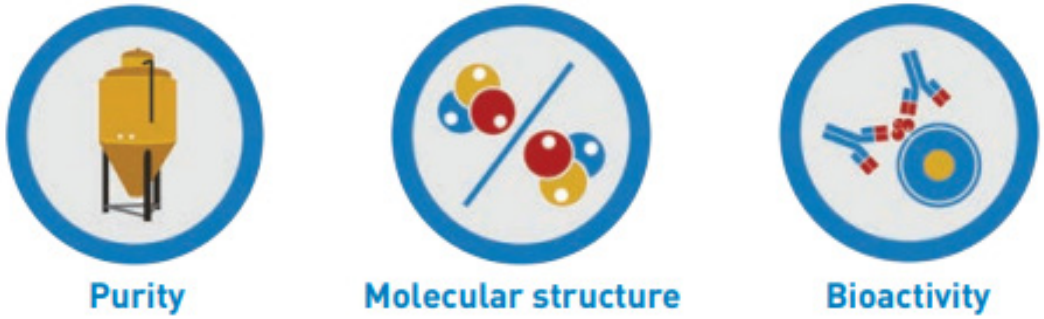
    - The abbreviated licensure pathway means manufacturer may rely, in part, on FDA's ***previous determination*** for the reference product.

      - Generally, biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials, potentially leading to faster access to these products. However, the biosimilar or interchangeable product is still subject to ***FDA's rigorous approval standards***.

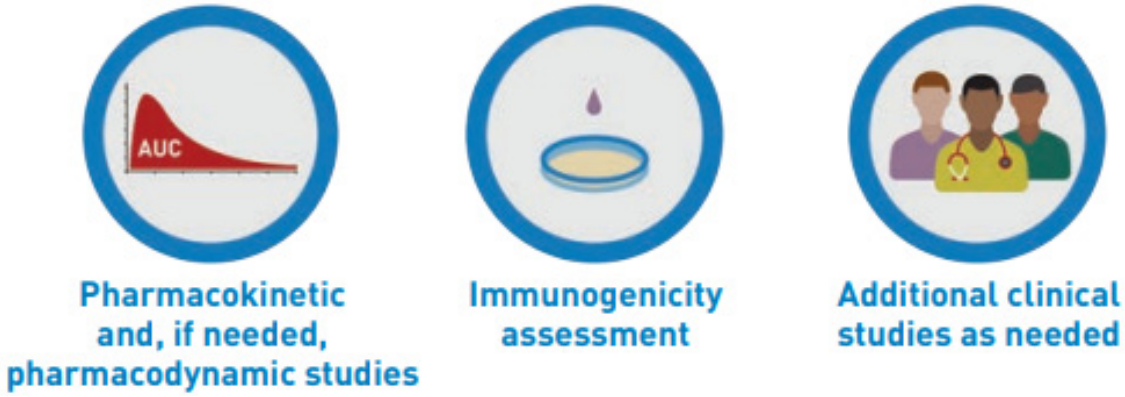
Demonstrating Biosimilarity

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.



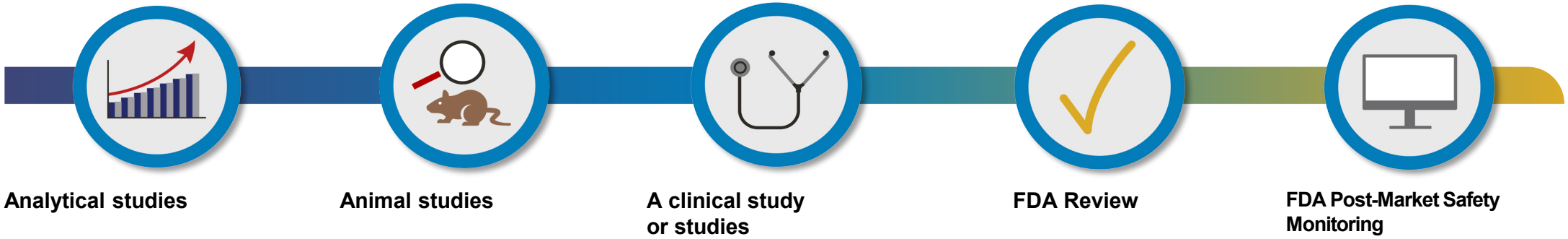
Demonstrating Biosimilarity

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.

Demonstrating Biosimilarity

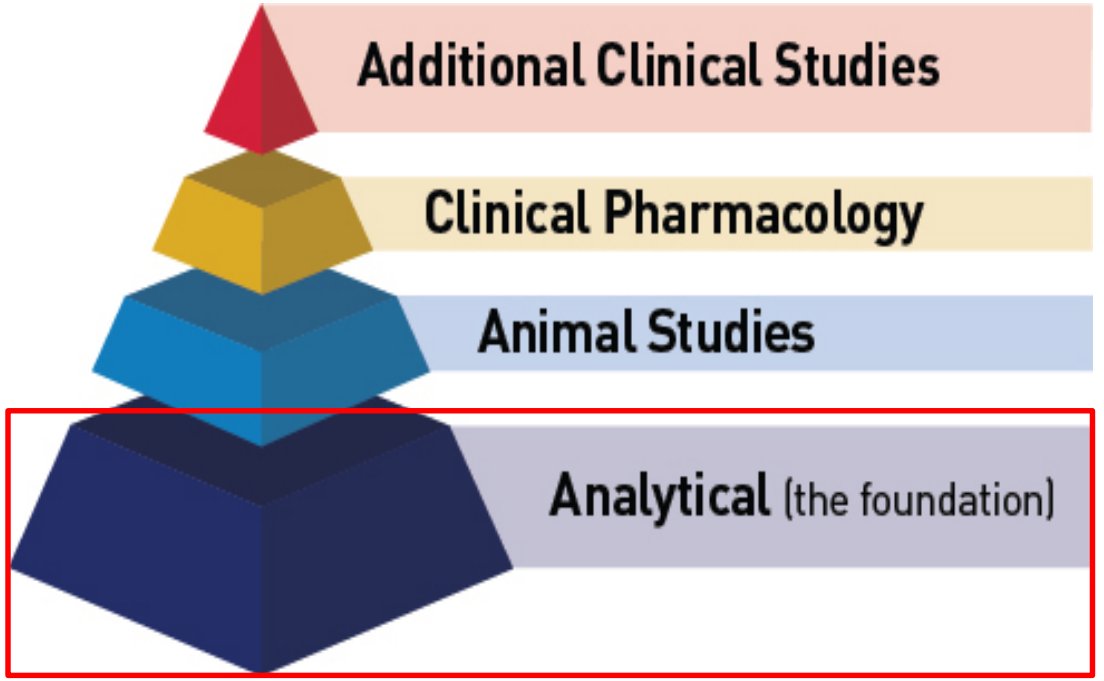
- ***Approval of a biosimilar product*** is based on the ***totality of the evidence*** submitted by the applicant to provide an overall assessment that the proposed product is biosimilar to the reference product.
- A demonstration supporting biosimilarity will be based upon data from: ***analytical studies, animal studies***, if any; and ***clinical study or studies***.
- 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 relevant animal studies, if any.



Comparative Analytical Data - The Foundation of a Biosimilar Development Program

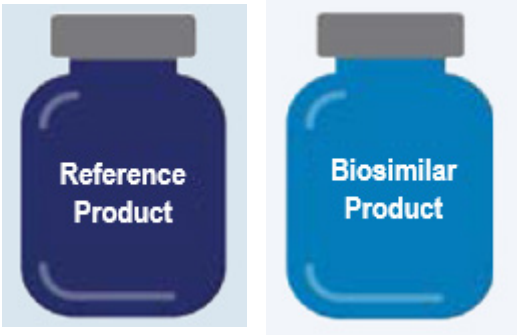
Extensive **structural and functional characterization**

- A biosimilar product with **similar structure and function** to the reference product should behave like the reference product (i.e., have **similar efficacy and safety** as the reference product)



Can Most Biologics be Copied Exactly? No

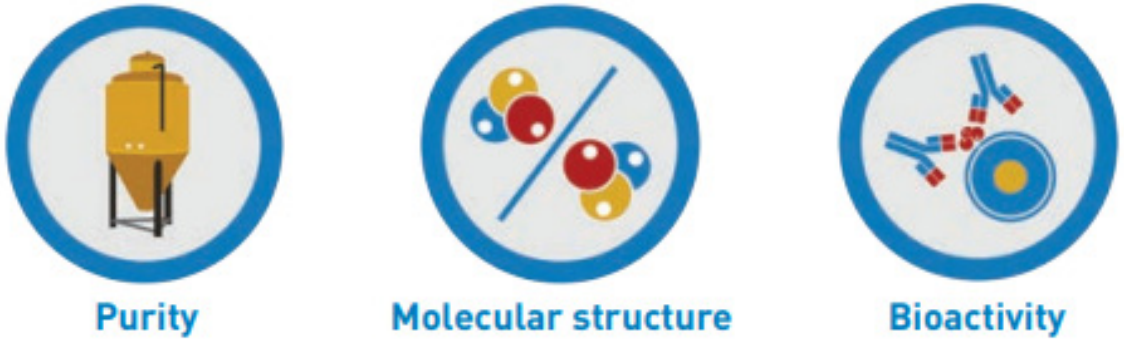
- Biologics are generally ***large, complex molecules***
- Most biologics are ***mixtures*** of variants
- Using advanced scientific analyses, molecular patterns and profiles emerge
- Biosimilars try to ***match the patterns and variations*** of the reference product
- Both the reference product and biosimilar contain these variants and try to keep a consistent mix



Comparative Analytical Assessment

- FDA draft guidance for industry “Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality Considerations” describes recommendations for the design and evaluation of ***comparative analytical studies***

- This guidance includes considerations for the development of a comparative analytical assessment plan, using a ***stepwise approach***, to support a demonstration of biosimilarity



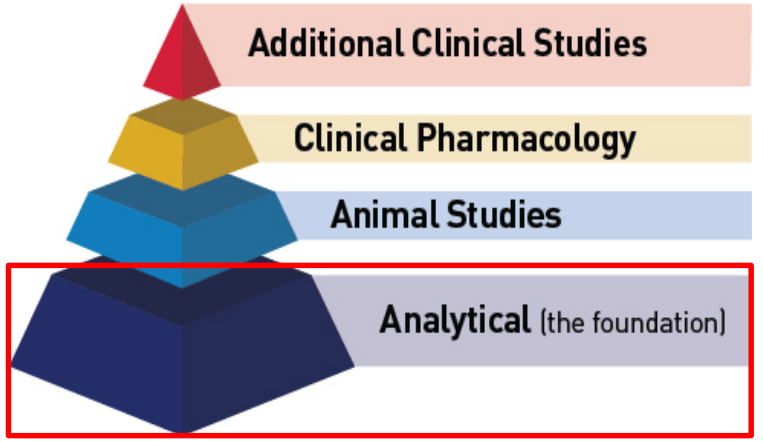
Comparative Analytical Assessment

Guidance provides clarity and flexibility for developers on:

- Analytical approaches to evaluating ***product structure and function***
- Updated recommendations for collection and analysis of ***comparative analytical similarity data***
- Receptiveness to considering ***alternative approaches*** proposed by sponsors for the analysis of analytical similarity data
- Aspects of the ***chemistry, manufacturing, and controls*** (CMC) portion (e.g., characterization, adventitious agent safety testing, process controls, specifications, and stability) of the marketing application

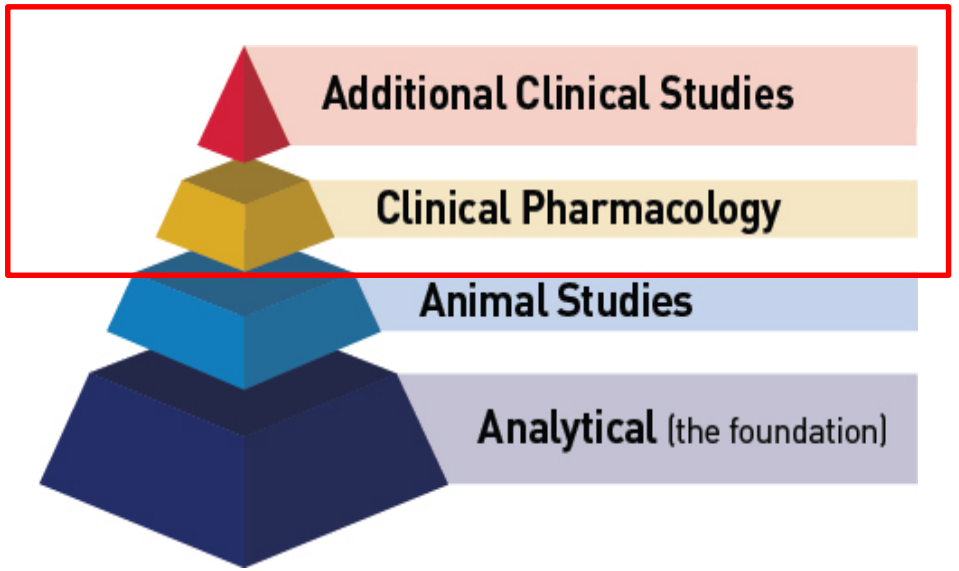
Comparative Analytical Assessment

- Comparative assessment of ***multiple physicochemical and biological attributes***
- Assays must be ***fit for purpose*** – able to detect differences if they exist
- Analyze ***multiple lots*** of the reference product and proposed biosimilar for each attribute:
  - Primary amino acid sequence
  - Biological activity - evaluation of attributes that affect known or presumed mechanism(s) of action
  - Post-translational modifications (glycosylation, phosphorylation, etc.)
  - Protein folding (higher order structure)
  - Heterogeneity (charge, size, aggregates, etc.)
  - Thermal and temporal stability
  - Impurities
  - Others



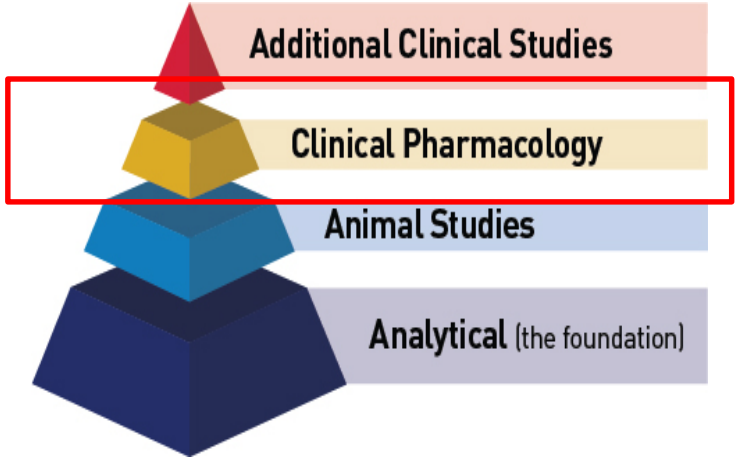
Role of Clinical Studies

- 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.
- See these FDA Guidance for Industry for recommendations on clinical studies
  - *Scientific Considerations in Demonstrating Biosimilarity to a Reference Product* (2015)
  - *Clinical Pharmacology Data to Support a Demonstration of Biosimilarity to a Reference Product* (2016)



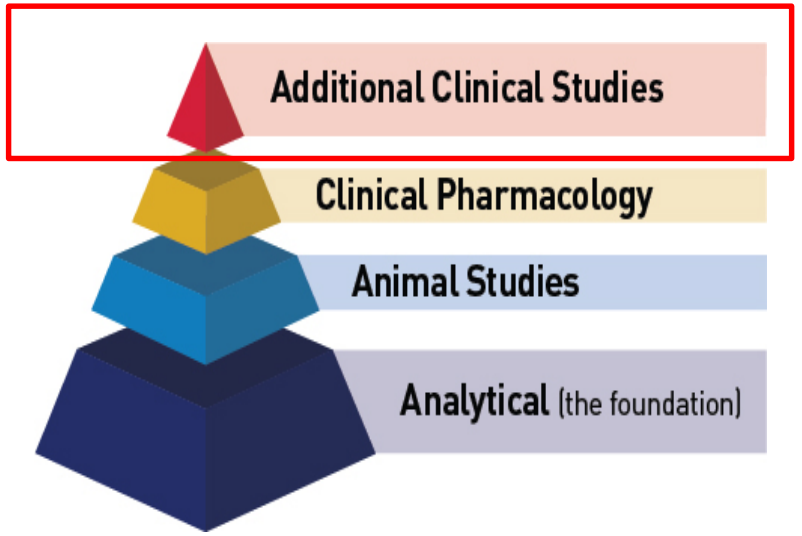
Comparative Human PK and PD Data

- 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 similarity*** in an adequately sensitive population to detect any differences
  - ***PD similarity*** 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

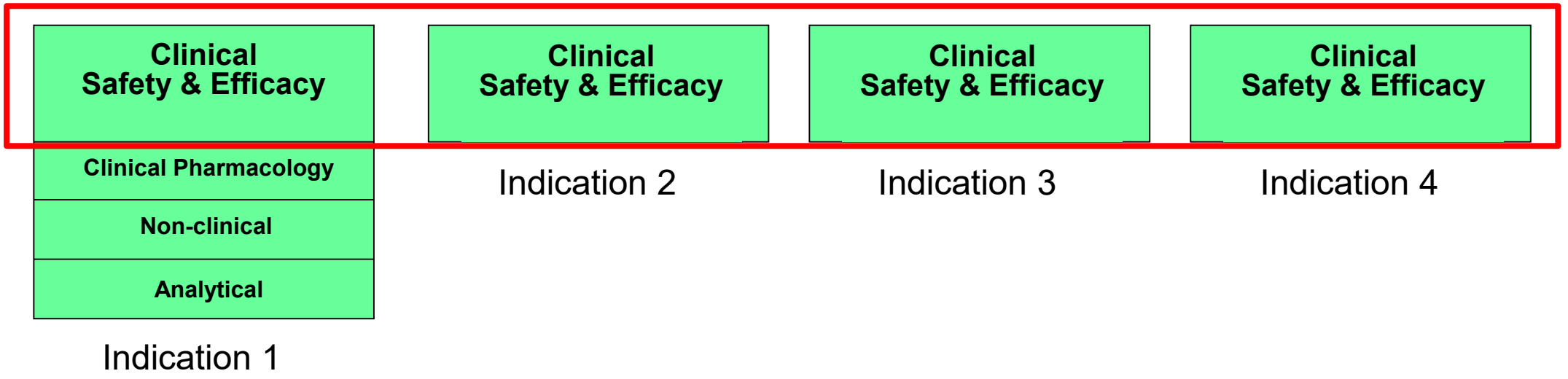
- A comparative clinical study for a biosimilar development program should be designed to investigate whether there are ***clinically meaningful differences*** in safety and efficacy between the proposed product and the reference product.
- Population, endpoint, sample size and study duration should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



Extrapolation

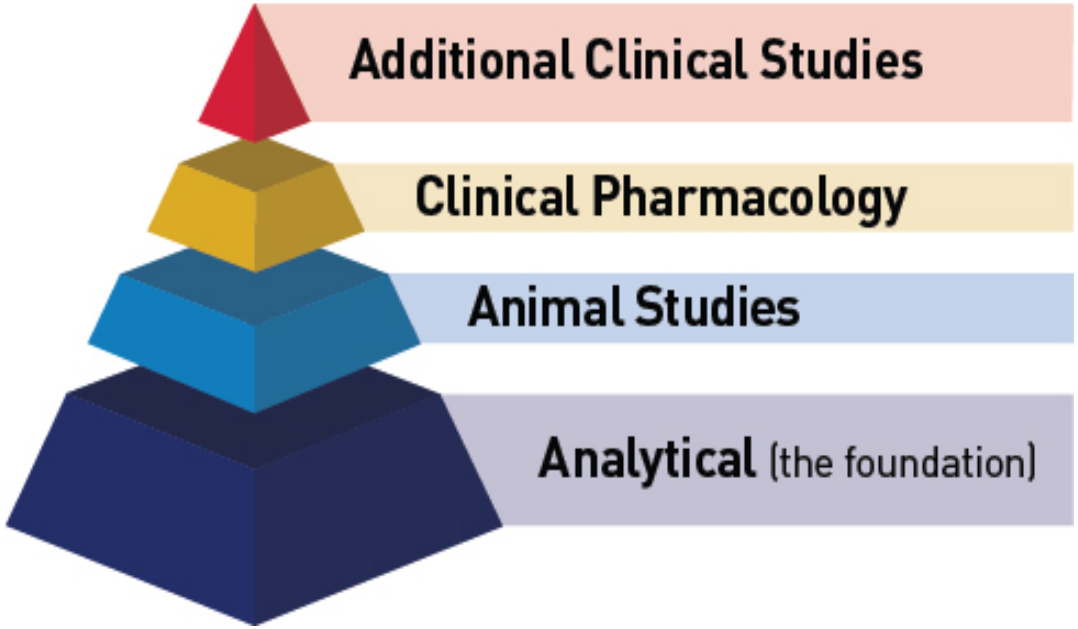
- A biosimilar product can approved for ***one or more additional conditions of use*** for which the reference product is licensed based on extrapolation
- FDA guidance outlines factors to consider, including:
  - ***MoA*** in each proposed condition of use
  - ***PK and biodistribution*** in different patient populations
  - ***Immunogenicity*** in different patient populations
  - Differences in ***expected toxicities*** in each condition of use and patient population
  - Any other factor affecting safety or efficacy in each proposed condition of use

Extrapolation Considerations: "Stand-alone" Drug Development



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

Indication 1	Indication 2	Indication 3	Indication 4
Clinical Safety & Efficacy	Clinical Safety & Efficacy	Clinical Safety & Efficacy	Clinical Safety & Efficacy
Clinical Pharmacology			
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

Interchangeability

- FDA guidance, “Considerations in Demonstrating Interchangeability With a Reference Product,” provides FDA’s current thinking on scientific considerations in demonstrating that a proposed biological product is interchangeable with a reference product.
- Outlines a ***stepwise approach*** to generate data
- ***Totality-of-the-evidence*** approach– no “one-size fits all” assessment
- Retained flexibility to provide space for the science in this area to evolve and for FDA to provide targeted advice on efficient study design in the context of product-specific meetings with prospective applicants.

Demonstrating Interchangeable Biosimilarity

1. The proposed interchangeable must be ***biosimilar to the reference product***.
2. The application must demonstrate that the proposed interchangeable "can be expected to produce the ***same clinical result*** as the reference product ***in any given patient***."
   - This will likely not involve additional clinical studies other than those necessary to support other elements of demonstrating interchangeability.

Demonstrating Interchangeable Biosimilarity, cont'd

3. For products administered more than once to a patient, information sufficient to show that "the ***risk in terms of safety or diminished efficacy of alternating or switching*** between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch."
   - To evaluate the risk, in terms of safety and diminished efficacy, of alternating or switching between the products, applications generally will include data from a switching study or studies in one or more appropriate conditions of use.

Demonstrating Interchangeable Biosimilarity, cont'd

- ***Switching studies***: Guidance outlines considerations for study design, including endpoints, design and analysis, study population, condition(s) of use, and routes of administration to be studied.
  - Option for sponsor to provide justification to FDA of why such data is not needed.
  - Switching studies generally not needed for biological products that are not intended to be administered to an individual more than once.

The Promise of Biosimilar and Interchangeable Products

FDA Approved Biosimilars

Year	Biosimilars Approved by FDA	
2020	**Hulio** (adalimumab-fkjb)	**Nyvepria** (pegfilgrastim-apgf)
2019	**Ontruzant** (trastuzumab-dttb)	**Ruxience** (rituximab-pvvr)
	Trazimera (trastuzumab-qyyp)	**Hadlima** (adalimumab-bwwd)
	Eticovo (etanercept-ykro)	**Ziextenzo** (pegfilgrastim-bmez)
	Kanjinti (trastuzumab-anns)	**Abrilada** (adalimumab-afzb)
	Zirabev (bevacizumab-bvzr)	**Avsola** (infliximab-axxq)
2018	**Retacrit** (epoetin alfa-epbx)	**Udenyca** (pegfilgrastim-cbqv)
	Fulphila (pegfilgrastim-jmdb)	**Truxima** (rituximab-abbs)
	Nivestym (filgrastim-aafi)	**Herzuma** (trastuzumab-pkrb)
	Hyrimoz (adalimumab-adaz)	
2017	**Renflexis** (infliximab-abda)	**Ogivri** (trastuzumab-dkst)
	Cyltezo (adalimumab-adbm)	**Ixifi** (infliximab-qbtx)
	Mvasi (Bevacizumab-awwb)	
2016	**Inflectra** (infliximab-dyyb)	**Amjevita** (adalimumab-atto)
	Erelzi (etanercept-szzs)	
2015	**Zarxio** (filgrastim-sndz)	

Reference Product	Approved = 28	Marketed = 17
Herceptin	5	5
Humira	6	0
Remicade	4	2
Neulasta	4	3
Neupogen	2	2
Avastin	2	2
Rituxan	2	2
Enbrel	2	0
Epogen	1	1

Highlighted = known or believed to be marketed

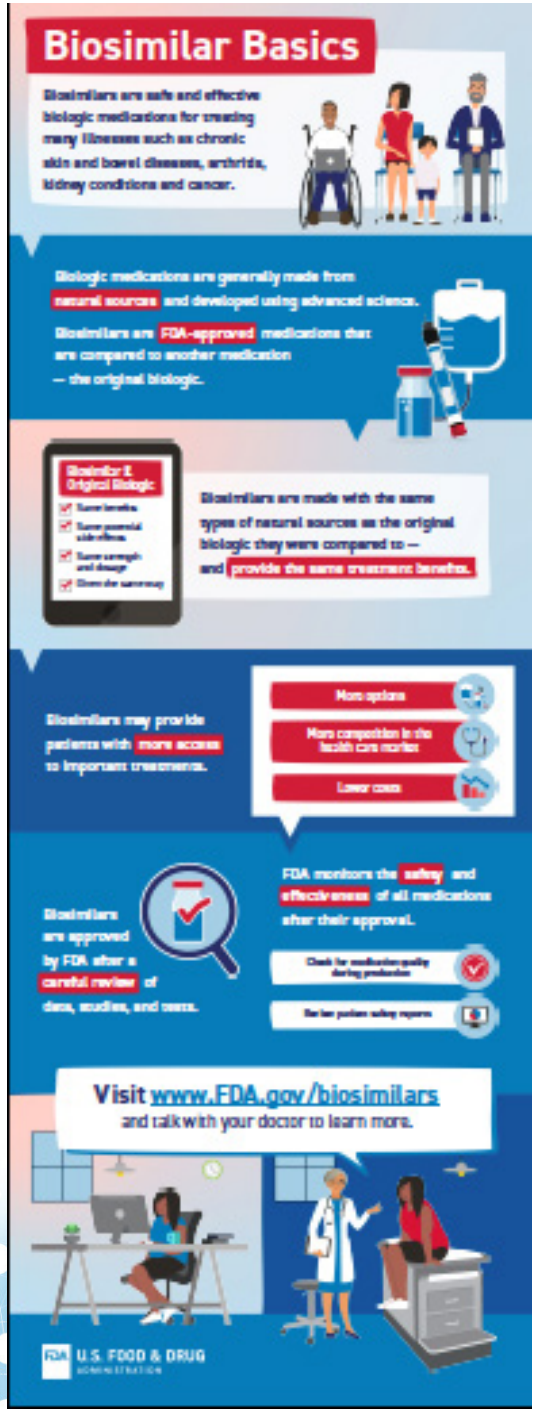
Find more information at www.FDA.gov/biosimilars

WHAT IS A **BIOSIMILAR?**

A biosimilar is a biological product

FDA-approved biosimilars have been compared to an FDA-approved biologic, known as the reference product. Reference and biosimilar products are:

- Generally large, complex molecules
- Produced from living organisms
- Carefully monitored to ensure consistent quality



New Purple Book Database

FDA created the Purple Book, AKA the "Database of FDA-Licensed Biological Products." The database provides patients, payors, clinicians, and others with an accessible, easy-to-use online search engine with more information about FDA-approved biological products, including biosimilar and interchangeable biological products.

The searchable database utilizes features tailored to different user needs, including:

- Main and advanced search options
- Auto-suggest search function
- Data download options
- Links to product labels
- Ability to show/hide sortable columns of information
- Ability to print or export search results

purplebooksearch.fda.gov/

Resources

Visit:

- www.fda.gov/biosimilars for access to all the education materials and information about biosimilar and interchangeable products.
- https://purplebooksearch.fda.gov/ The Purple Book: Database of Licensed Biological Products for information on biological products, including if products are biosimilar to a reference product.
- www.fda.gov/drugsatfda (**Drugs@FDA**) for information on all FDA approved drug products, including labeling and review information.
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents for links to FDA guidance for industry
- https://www.fda.gov/advisory-committees/committees-and-meeting-materials/human-drug-advisory-committees for drug advisory committee meetings and materials related to biosimilars.