Biosimilar and Interchangeable Biological Products:
Basic Concepts and Practical Resources

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Overview

- Background and Progress To Date
  - Biosimilars Action Plan
- Introduction to Biosimilarity Concepts
  - Basics of Biosimilarity
- FDA's Approach to the Development of Biosimilars
- Using Biosimilar and Interchangeable Products
- Resources for Health Care Providers

Learning Objectives

1. Describe how biologics differ from small molecules
2. Explain why some biologics cannot be copied exactly
3. Compare and contrast the development and approval process for new biologics and biosimilars/interchangeables
4. Recognize the differences in the statutory requirements for approval between new biologics and biosimilars or interchangeables
5. Describe and explain the resources available for health care provider to learn more about biosimilar and interchangeable products through the Purple Book and other resources.

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Background and Progress To Date

Biosimilars Action Plan (BAP)

1. Improving the efficiency of the biosimilar and interchangeable product development and approval process

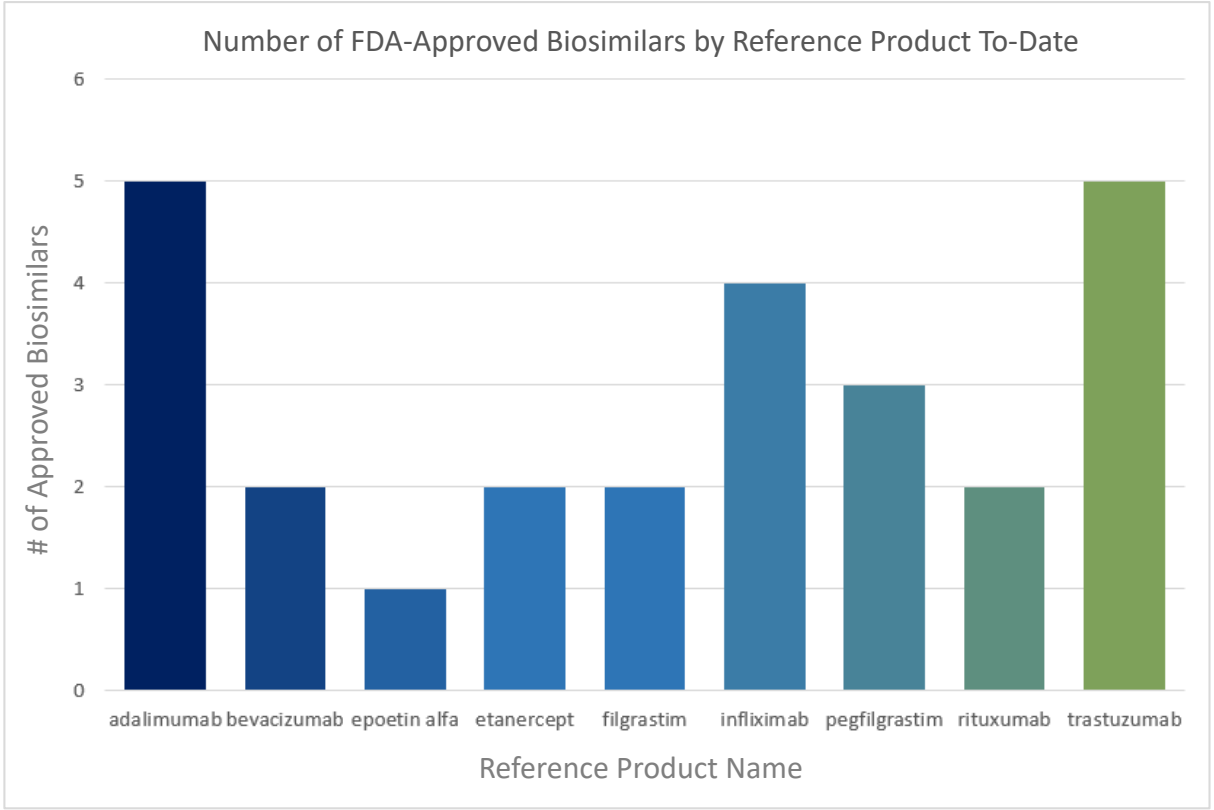
2. Maximizing scientific and regulatory clarity for the biosimilar product development community

3. Developing effective communications to improve understanding of biosimilars among patients, clinicians and payors

4. Supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay competition

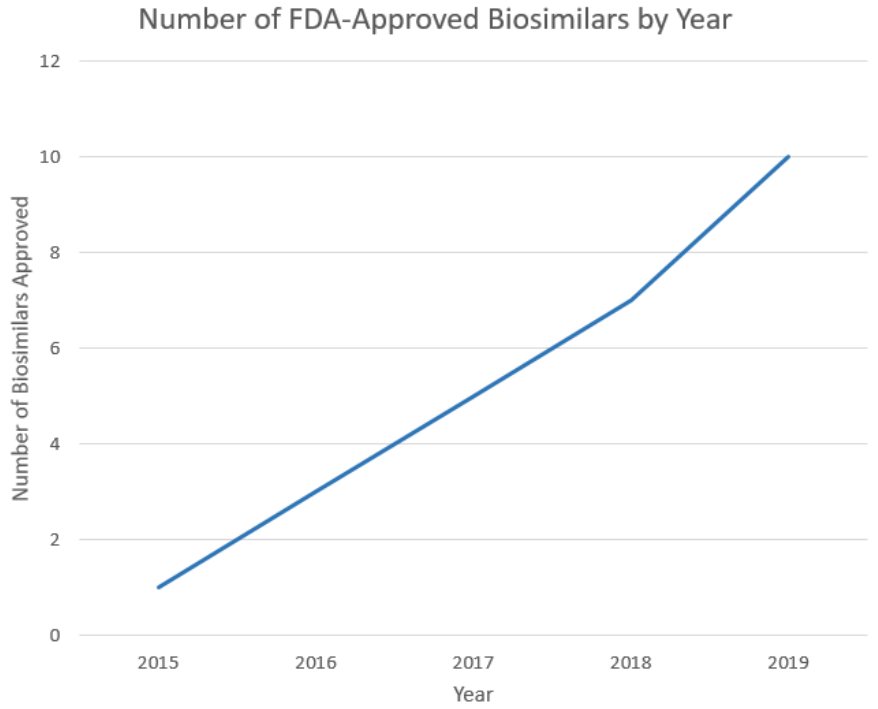
Biosimilars: 2019 Year in Review

Biosimilars Approved by FDA in 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)



Biosimilars: 2019 Year in Review (cont.)

- As of December 2019:
  - **26** 351(k) BLAs for biosimilar products have been approved
  - **74** programs enrolled in the Biosimilar Product Development (BPD) Program
  - **12** companies publicly announced submission of **30** 351(k) BLAs to FDA
  - CDER received meeting requests to discuss the development of biosimilars for **38** different reference products



Biosimilars: 2019 Year in Review (cont.)

Completed Activities

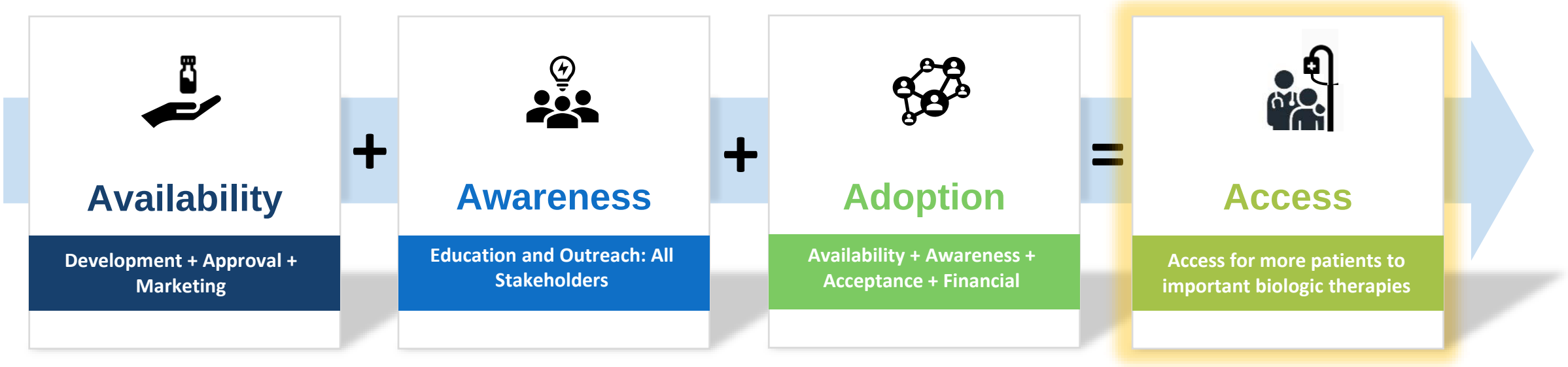
- Established the Office of Therapeutic Biologics and Biosimilars
- Published article on "Advancing biosimilar development using Pharmacodynamic (PD) Biomarkers in Clinical Pharmacology Studies"
- Held Public Hearing on "The Future of Insulin Biosimilars"
- Released Draft Guidances:
  - "Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations"
  - "Nonproprietary Naming of Biological Products: Update"
  - "Clinical Immunogenicity of Biosimilar and Interchangeable Insulin Products"
- Released Final Guidance:
  - "Considerations in Demonstrating Interchangeability with a Reference Product"
- Released "Biosimilar Basics" for patients
- Stakeholder Meetings
- Other Engagement Activities

Key In-Progress Activities

- Enhance the Purple Book
- Provide product developers with information resources and development tools
- Develop additional biosimilars educational resources
- Develop standardized review templates specific to 351(k) BLAs
- Identify and develop additional guidances
- Oversee the transition of biological products

Supporting a competitive marketplace

Solving The Equation for Patient Access



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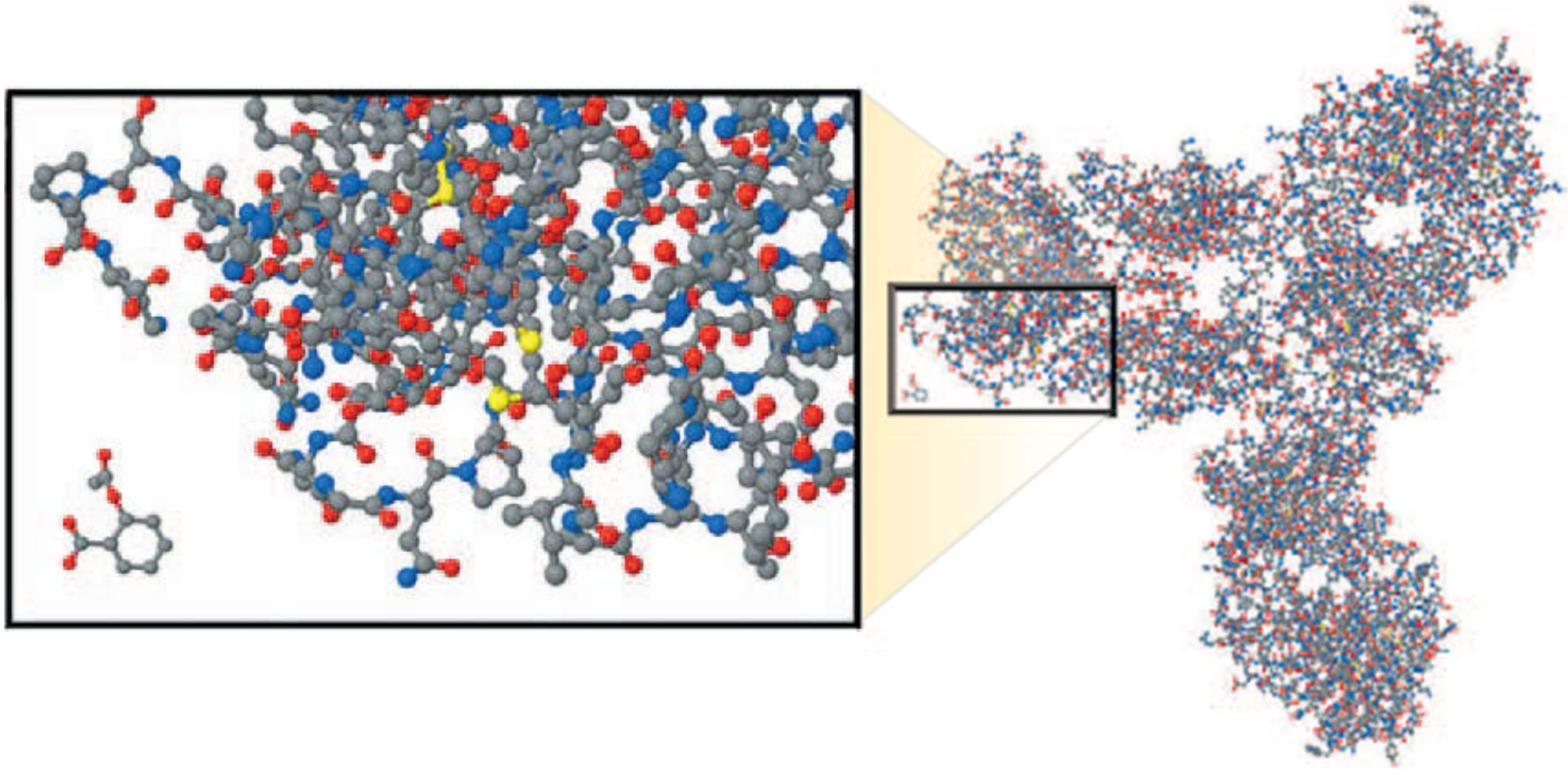
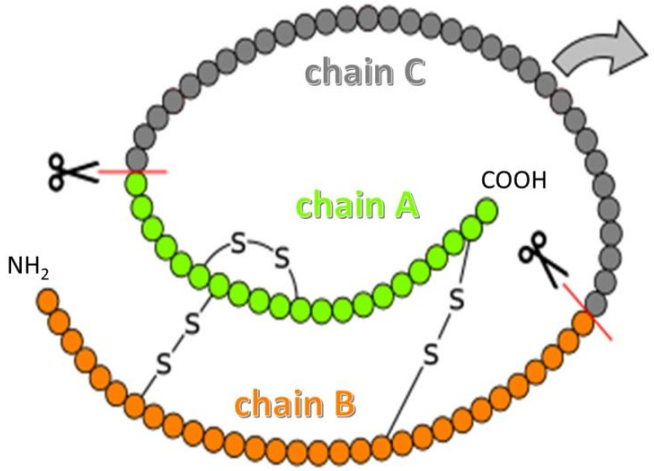
Introduction to Biosimilarity Concepts

Biologics vs. Small Molecules

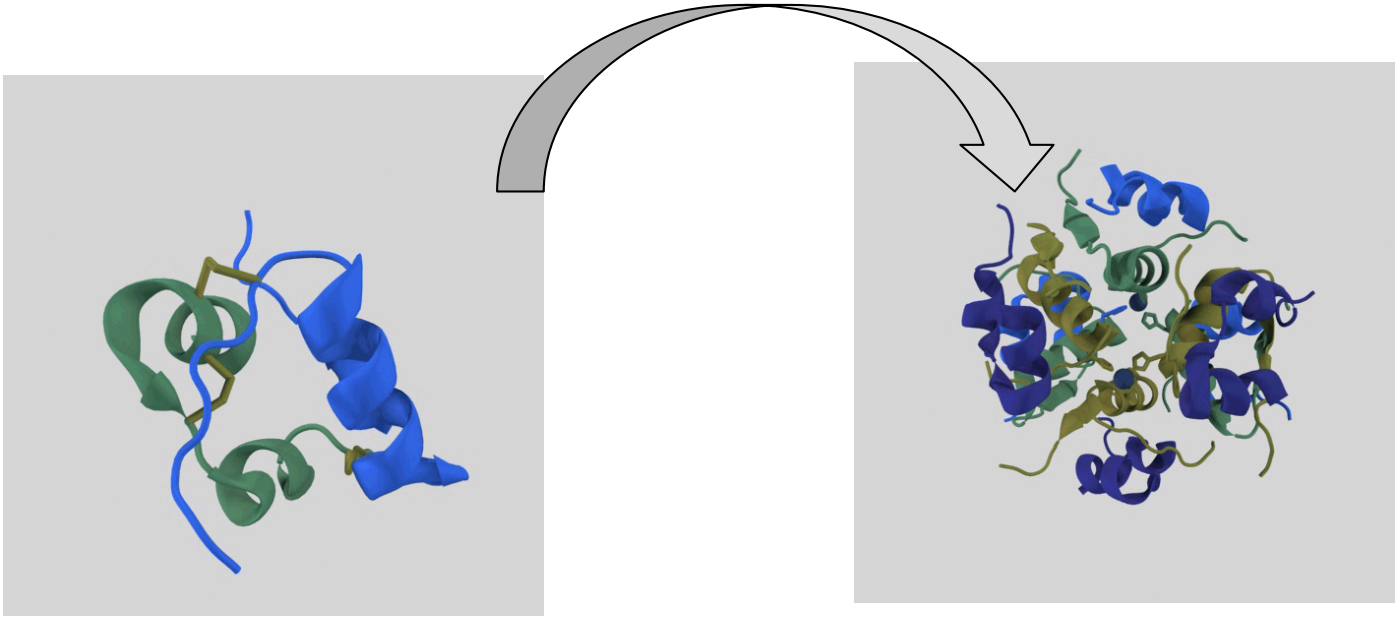


mAB versus Aspirin molecule. Kozlowski, S et. Al, NEJM 2011, 385

The Spectrum of Biologic Complexity: Insulin



Pro-Insulin
Chain A = Green;
Chain B = Orange
S-S = disulfide bridges

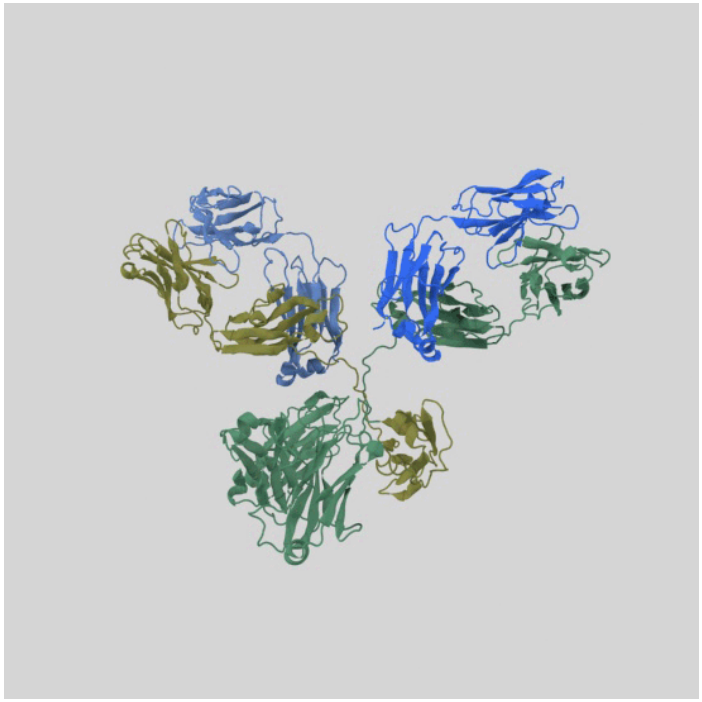


Insulin
Chain A = Blue (21 aa);
Chain B = Green (30 aa)
Olive green = disulfide bridges
Nonglycosylated

Structure: Simple
Complexity: tendency to aggregate and immunogenicity

Media source: Theis K, Harel M, Prilusky J, Canner D
proteopedia.org/wiki/index.php/Insulin

The Spectrum of Biologic Complexity: mAbs

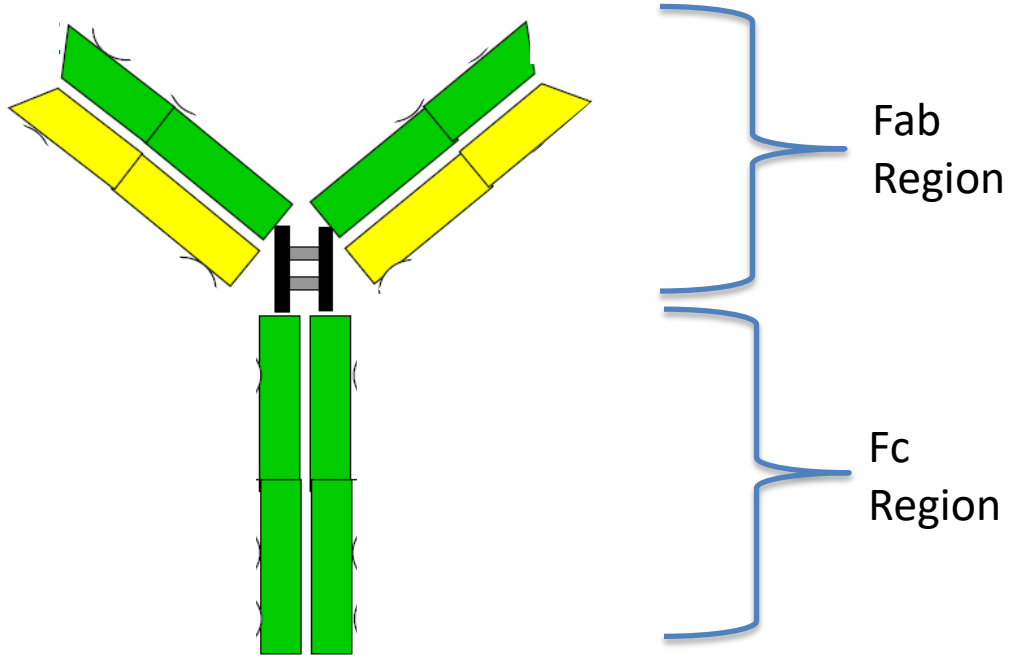


Monoclonal Antibodies
Heavy Chain x 2 = 50 kDa
Light Chain x 2 = 25 kDa
Total Molecular Weight ≈ 150 kDa

- Structure: Complex
- Large (i.e., 150 kDa) proteins with four separate chains
- "Fab" Region: Specific antigen binding sites for specificity
- "Fc" Region: Potential additional effects on function and exposure

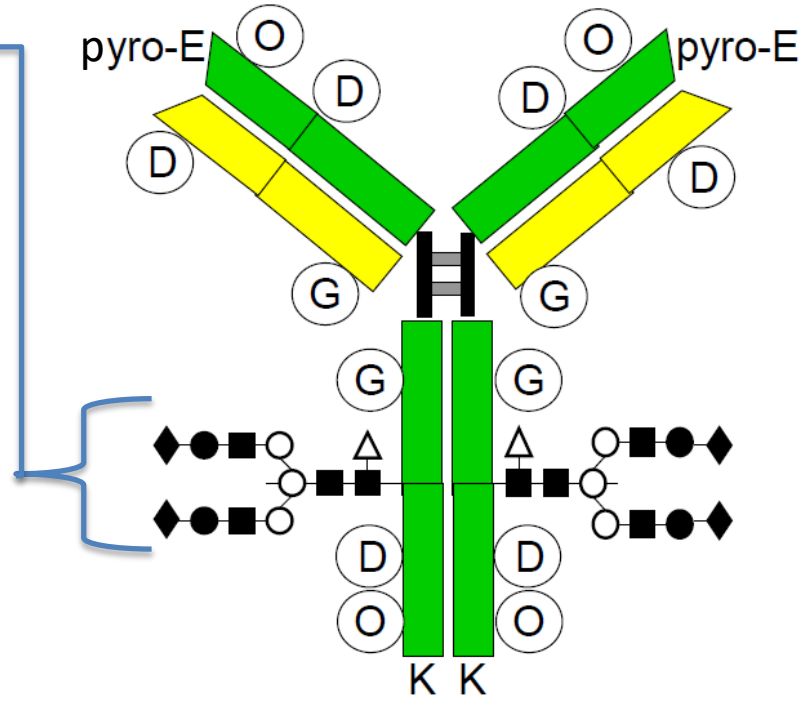
The Spectrum of Biologic Complexity: Modifications

- Biosimilars and the original biologics they are referencing will have the same underlying amino acids and proteins
- So why can't they all be called "identical" or "copies"?
- "Add-ons" and modifications to certain amino acids



The Spectrum of Biologic Complexity: Modifications

- Glycosylation, typically a variety, within certain ranges
- Result: Millions of slightly different versions of the same protein or antibody per dose or batch
- Both reference products and biosimilars contain these variations
- Biosimilars try to match the patterns and variations of the reference product



Pyro-Glu (2)

Deamidation (3 x 2)

Methionine oxidation (2 x 2)

Glycation (2 x 2)

High mannose, G0, G1, G1, G2 (5)

Sialylation (5)

C-terms Lys (2)

Total variants $(9600)^2 \approx 10^8$

2 x 6 x 4 x 4 x 5 x 5 x 2 = 9600

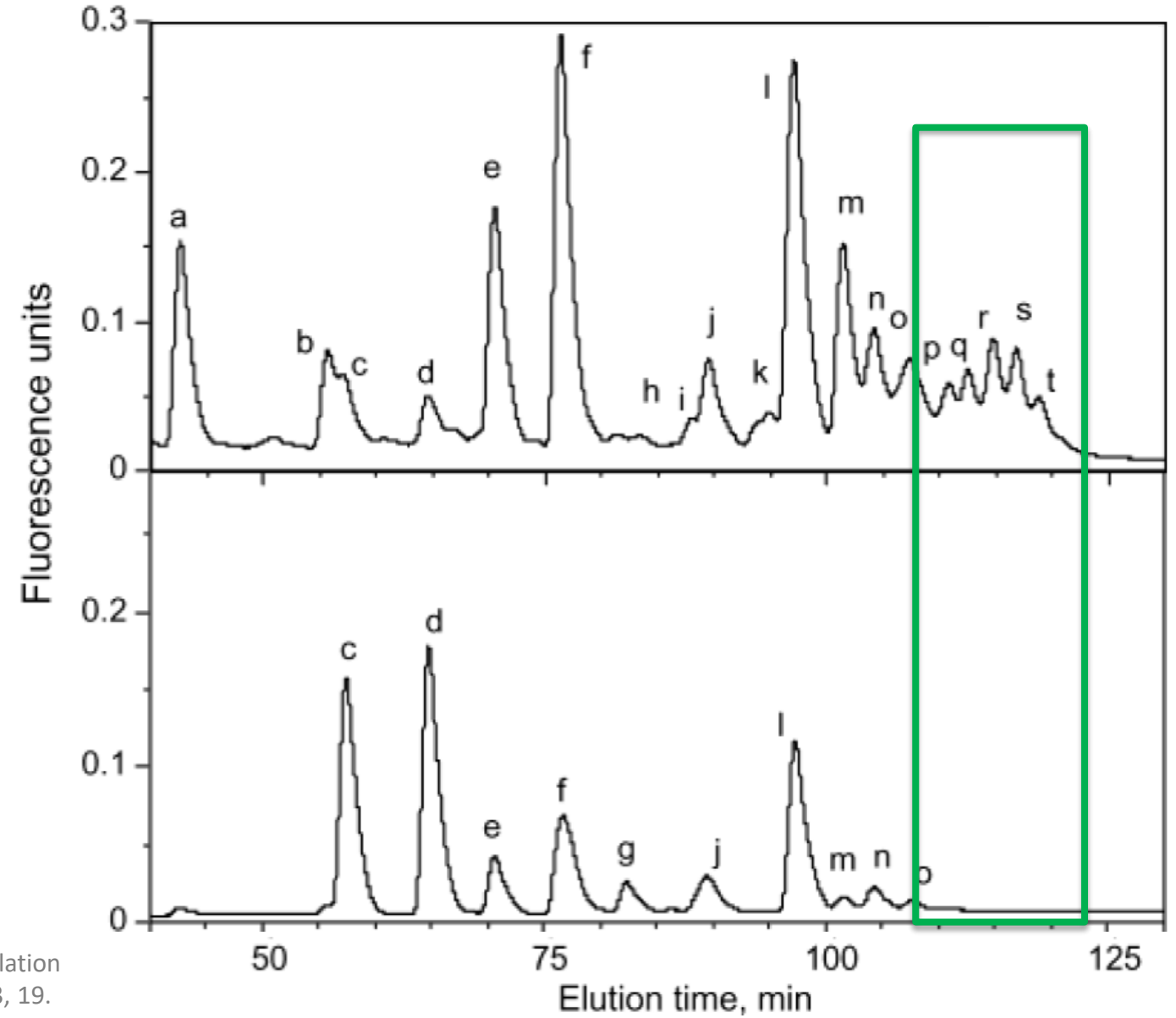
Glycosylation Differences: Type

Questions:

1. Will difference predispose to an immune reaction?

2. Will difference result in different exposure?

3. Will difference result in different activity?



*These graphs are for illustration purposes only and were not from pharmaceutical samples.

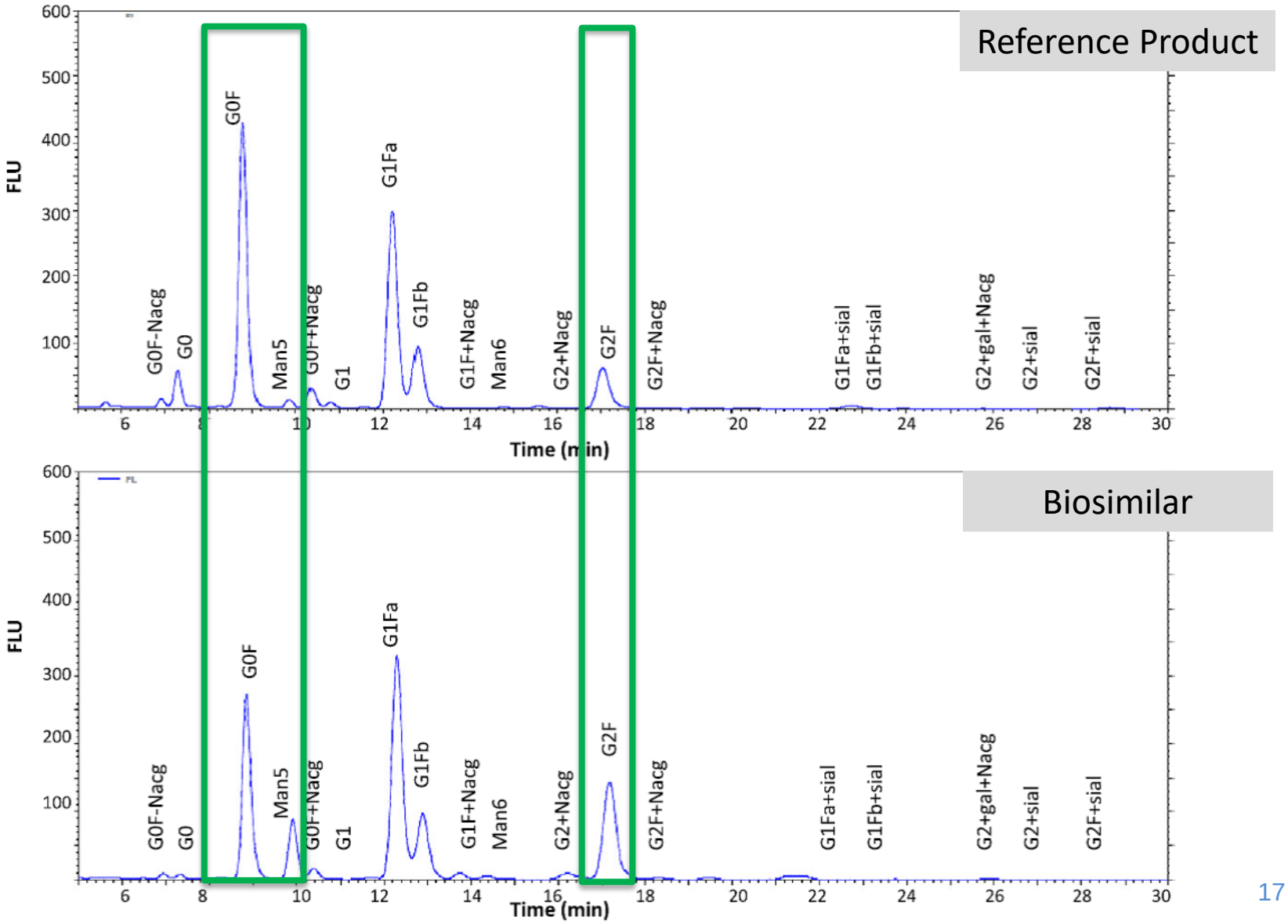
Novel Insect Cell Line Capable of Complex *N*-Glycosylation and Sialylation of Recombinant Proteins, Palomares, L et al., Biotechnol. Prog. 2003, 19.

Glycosylation Differences: Amount

Questions:

1. Will difference result in different exposure?

2. Will difference result in different activity?



N-glycosylation profile analysis of Trastuzumab biosimilar candidates by Normal Phase Liquid Chromatography and MALDI-TOF MS approaches, Melo, IS et al., Journal of Proteomics 2015, 125.

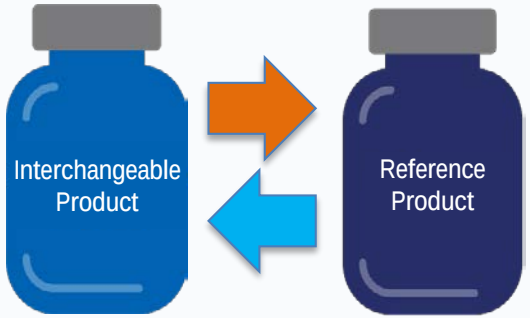
Basics of Biosimilarity

Reference Product

A reference product is the single biological product, already approved by FDA, against which a proposed biosimilar product is compared

Biosimilar Product

A biosimilar is a biological product that is **highly similar and has no clinically meaningful differences** from an existing FDA-approved reference product

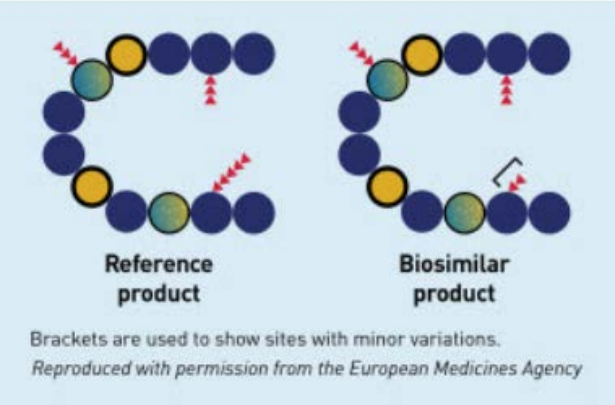


Interchangeable Product

An interchangeable is a biosimilar product that can be substituted for the reference product without the intervention of the prescribing health care provider

What does it mean to be “highly similar”?

- The proposed biosimilar product is shown to be highly similar to the reference product by extensively analyzing (i.e., characterizing) the structure and function of both the reference product and proposed biosimilar.



What does it mean to have “no clinically meaningful differences”?

- The proposed biosimilar product has no clinically meaningful differences from the reference product in terms of **safety**, **purity**, and **potency** (safety and effectiveness)

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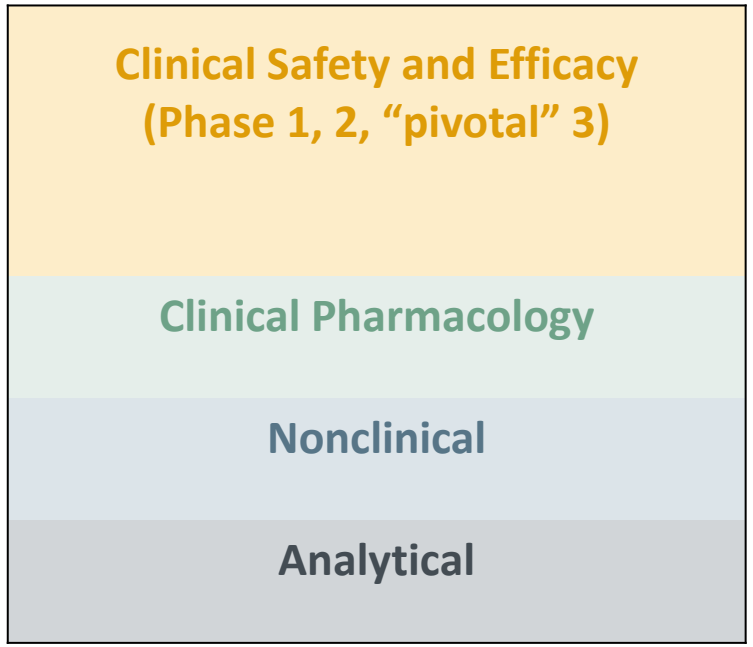
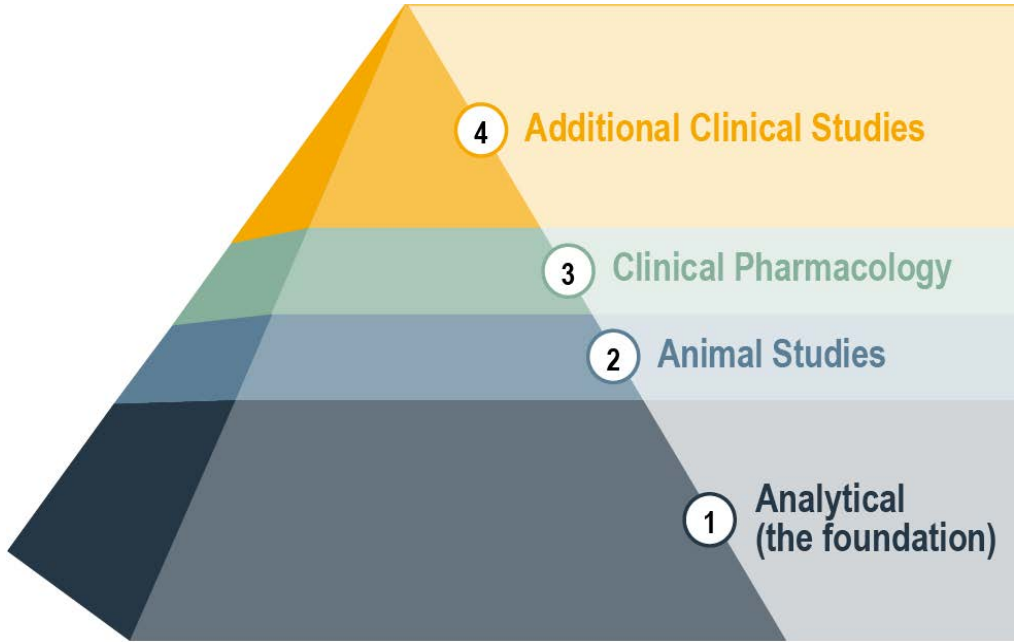
FDA's Approach to the Development of Biosimilars

Different Goals for "Stand-alone" vs. Biosimilar Development

"Stand-alone": 351(a) BLA
Goal: To establish *de novo* safety and efficacy of a new product



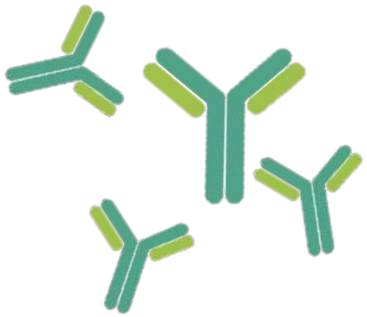
"Abbreviated": 351(k) BLA
Goal: To demonstrate biosimilarity (or interchangeability) to a reference product

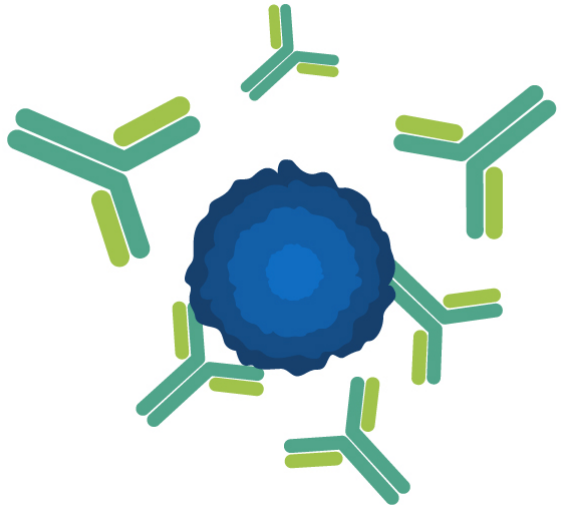


What does this difference mean from a development perspective?

Immunogenicity

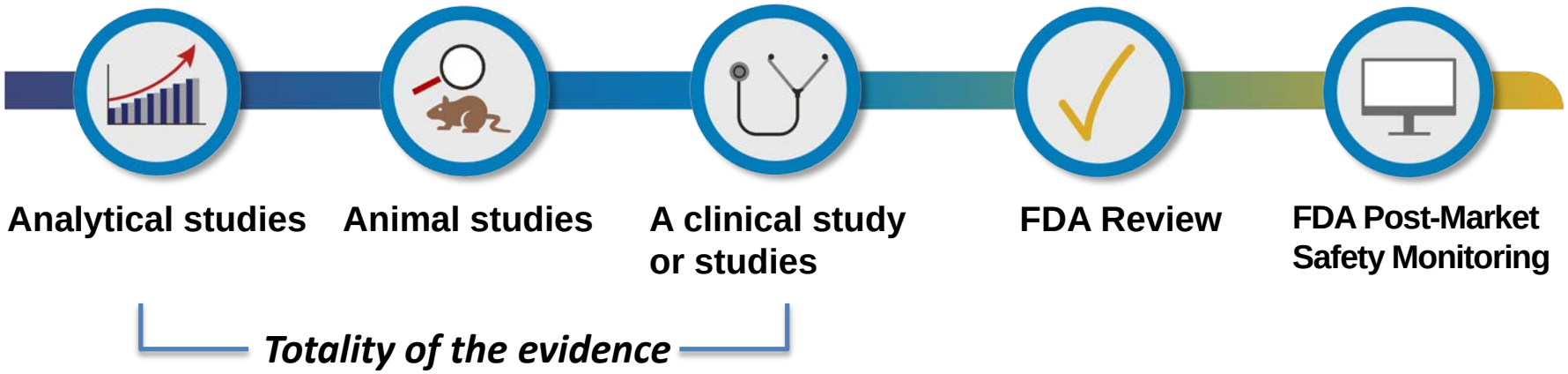
- Immunogenicity refers to the potential for the body to elicit an immune reaction in response to a biological product, which, in rare cases, may result in decreased efficacy of the product
- Biological products, including both reference products and biosimilar products, have a small risk of immunogenic response
- Biosimilar products are expected to have the same rate of immunogenic response as the reference product





Summary

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



Approval 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 the reference product.

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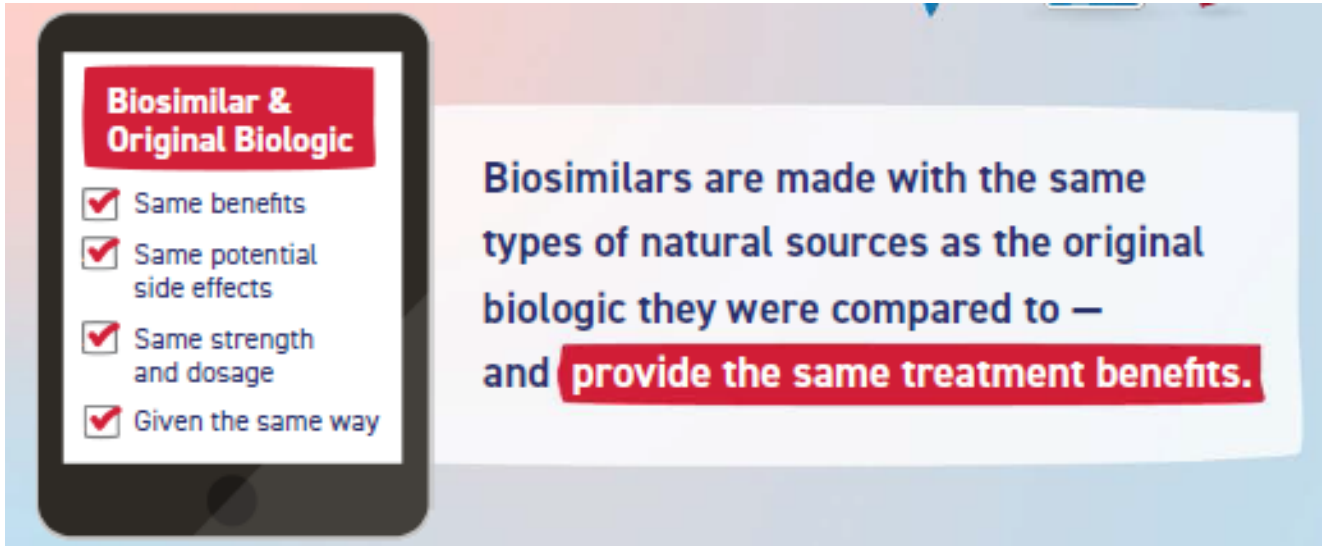
Using Biosimilar and Interchangeable Products

Using Reference, Biosimilar, and Interchangeable Products

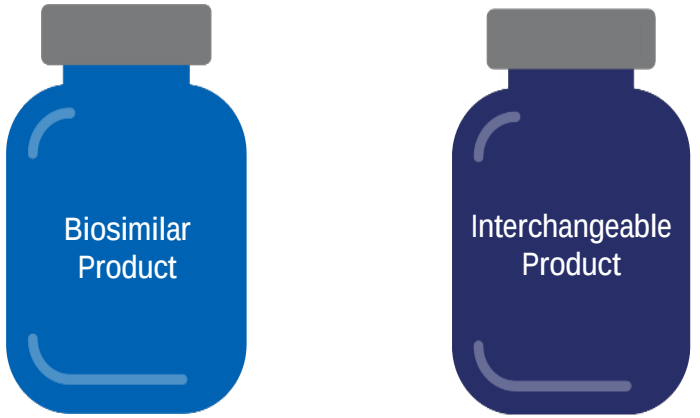
- Patients and health care providers *can be confident in the **safety** and **effectiveness** of a biosimilar product* as for the reference product.
  - All approved reference products and biosimilar products meet FDA's *rigorous standards* for the indications described in product labeling.

- Once available in the U.S., states may permit a pharmacist to substitute an interchangeable product for the reference product without consulting the prescriber.



What to expect with a Biosimilar?

- Approved prescribing information summarizes the scientific information health care practitioners need for safe and effective use of the product.
- Labeling:
  - The Highlights Section contains a “Biosimilarity Statement” describing the biosimilar product’s relationship to its reference product
  - A biosimilar product is not required to have the same labeling as its reference product. Biosimilar product labeling may differ from the reference product labeling for a variety of reasons
  - **For specific product information, visit Drugs@FDA**



Key Takeaways

- ***Fact:*** FDA's high standards for approval means healthcare professionals and patients can be confident in the safety and effectiveness of a biosimilar product.
- ***Fact:*** Minor differences between the biosimilar and reference product are expected due to their complexity but generally do not result in clinically meaningful differences.
- ***Fact:*** Biosimilar labeling is not required to be the same as the reference product, but will often be similar.
- ***Fact:*** FDA's approval of an interchangeable biological product does not indicate a higher standard of biosimilarity.
- ***Fact:*** Patients and healthcare providers do not need to wait for a biosimilar product to "become" an interchangeable product (as there may be business reasons a sponsor does not seek interchangeability). Biosimilars are safe and effective, just like the reference product they were compared to.

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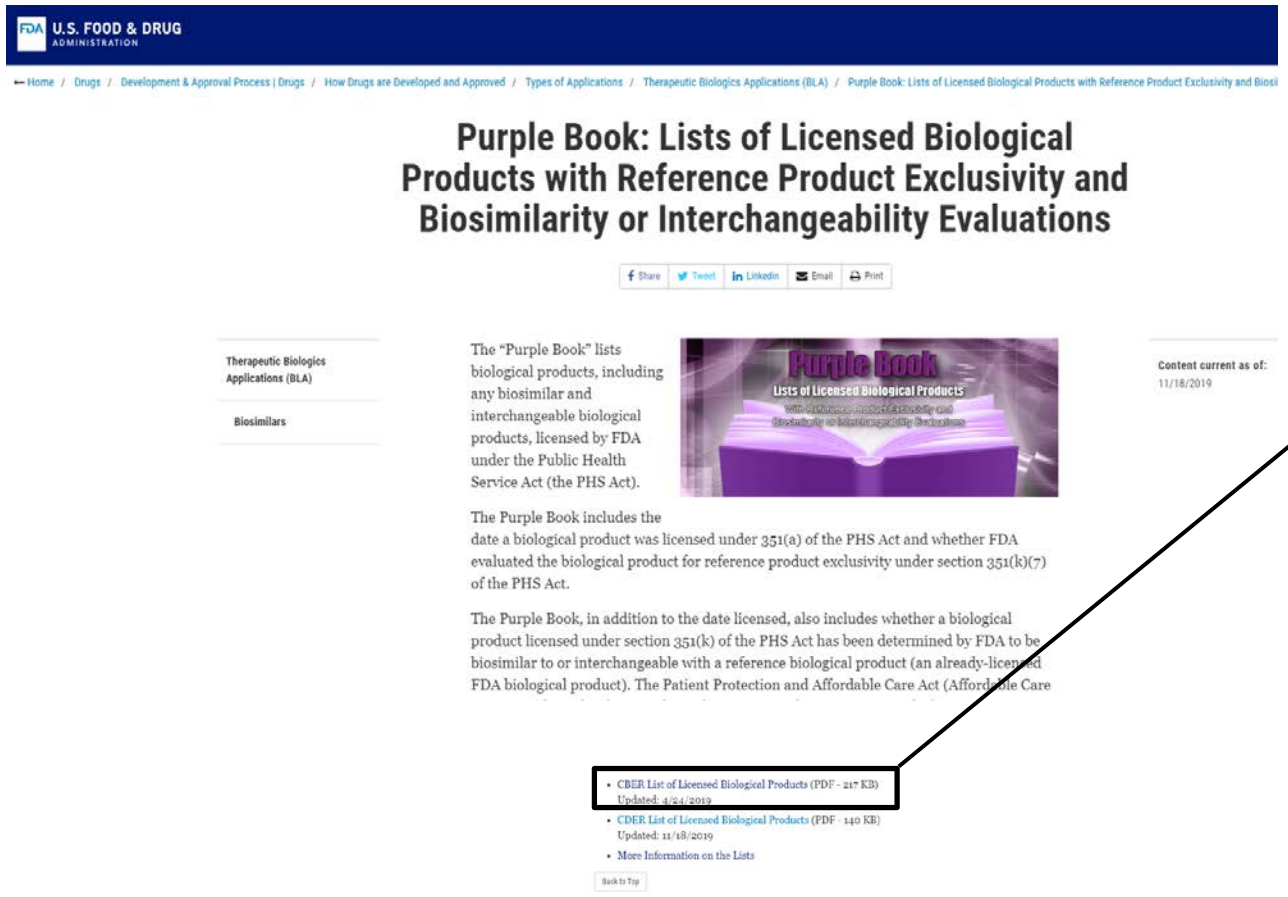
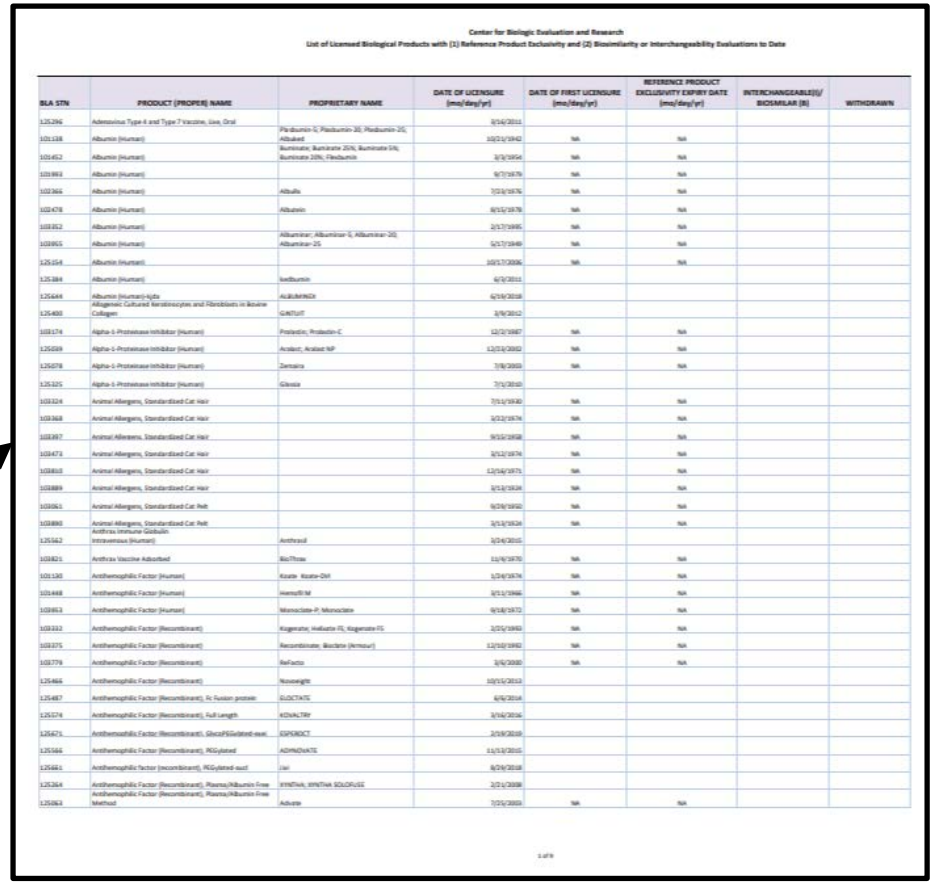
Resources for Health Care Providers

Purple Book

Currently, the Purple Book is available as a PDF format on FDA.gov.





The new Purple Book database

FDA is working to digitize and expand the “Purple Book: Database of FDA-Licensed Biological Products” to:

- Improve transparency around approved biological product options
- Expand database access and functionality for users
- Advance public awareness about biosimilar products

Purple Book Database's New Features

The future database will provide 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 will utilize new features tailored to different user needs, including:

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

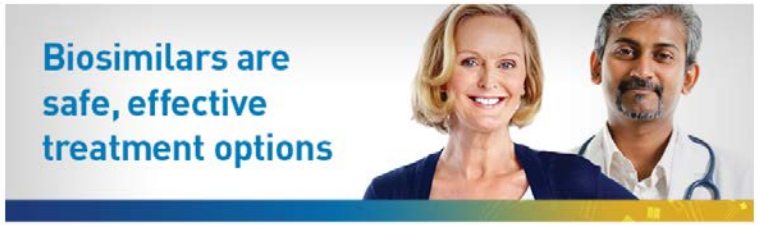
Education and Outreach

- FDA is committed to developing materials and resources to improve understanding of biosimilars among patients, health care providers, and payors:
  - Engaging with health care professional and patient stakeholders
  - Developing educational materials for health care prescribers, pharmacists, and patients
  - Education is an undertaking that requires multi-stakeholder engagement

- FDA offers a variety of outreach materials for health care providers and patients:
  - Website with information for health care providers and patients
  - Health Care Professional Toolkit (4 Fact sheets, Infographics)
  - Webinars, Presentations and Articles
  - Video Series
  - Patient Materials

- Visit www.fda.gov/biosimilars

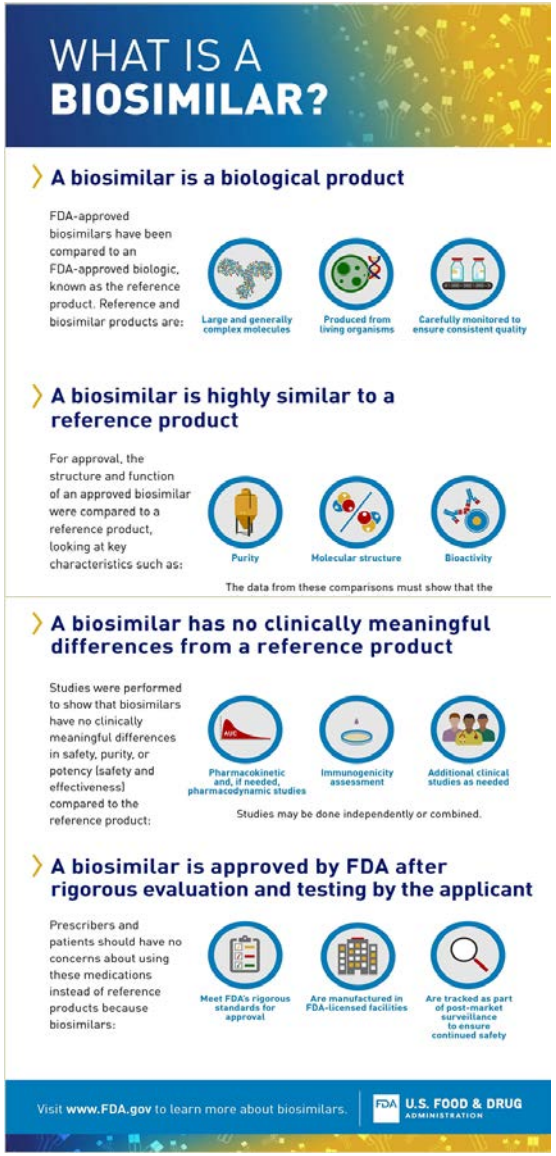
Health Care Provider Materials



Congress, through the Biologics Price Competition and Innovation Act (BPCI Act) of 2009, created an abbreviated licensure pathway for biological products that are demonstrated to be biosimilar to or interchangeable with an FDA-approved biological product. This pathway was established as a way to provide more treatment options, increase access to lifesaving medications, and potentially lower health care costs through competition.

Biosimilars Action Plan (BAP)

New Educational Materials
Learn more about biosimilars and check out our videos, fact sheets, shareable graphics, and other new resources



Patient Materials

- Uses patient-friendly language and imagery
- Addresses topics, concerns, and misconceptions shown to be most important to patients
- Tested with patient advocacy organizations and with patients treated with a biologic

Future Education and Outreach Plans

- Continue developing materials and resources for patients:
  - Videos
  - Additional infographics and graphics
  - Enhanced Social Media Strategy

- Create additional materials and resources for health care providers:
  - One-pager to address misconceptions
  - Educational curriculum/teaching resources for medical, nursing, and pharmacy schools
  - Updated Continuing Education Course

- Develop and revise materials as needed based on research/feedback

Resources

- Visit www.fda.gov/biosimilars for access to all the education materials and information about biosimilar and interchangeable products

- Visit the www.fda.gov/purplebook for information on biological products, including if products are biosimilar to a reference product

- Visit www.fda.gov/drugsatfda (**Drugs@FDA**) for information on all FDA approved drug products, including labeling and review information.

References

1. FDA website: www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval
2. Purple Book: www.fda.gov/purplebook
3. Gramer MJ, “Product quality considerations for mammalian cell culture process development and manufacturing.” Adv Biochem Eng Biotechnol 2014, 139:123-166
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6. Berkowitz SA, Engen JR, Mazzeo JR, Jones GB, “Analytical tools for characterizing biopharmaceuticals and the implications for biosimilars.” Nat Rev Drug Disc. July 2012; 11:527-540

Questions?

Thank You

www.fda.gov/biosimilars