

# Biosimilar and Interchangeable Biological Products: Basic Concepts and Practical Resources

**Sarah Yim, M.D., Acting Director**  
**Leila Hann, Science Policy Analyst**  
Office of Therapeutic Biologics and Biosimilars  
CDER/FDA



# 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.

# 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

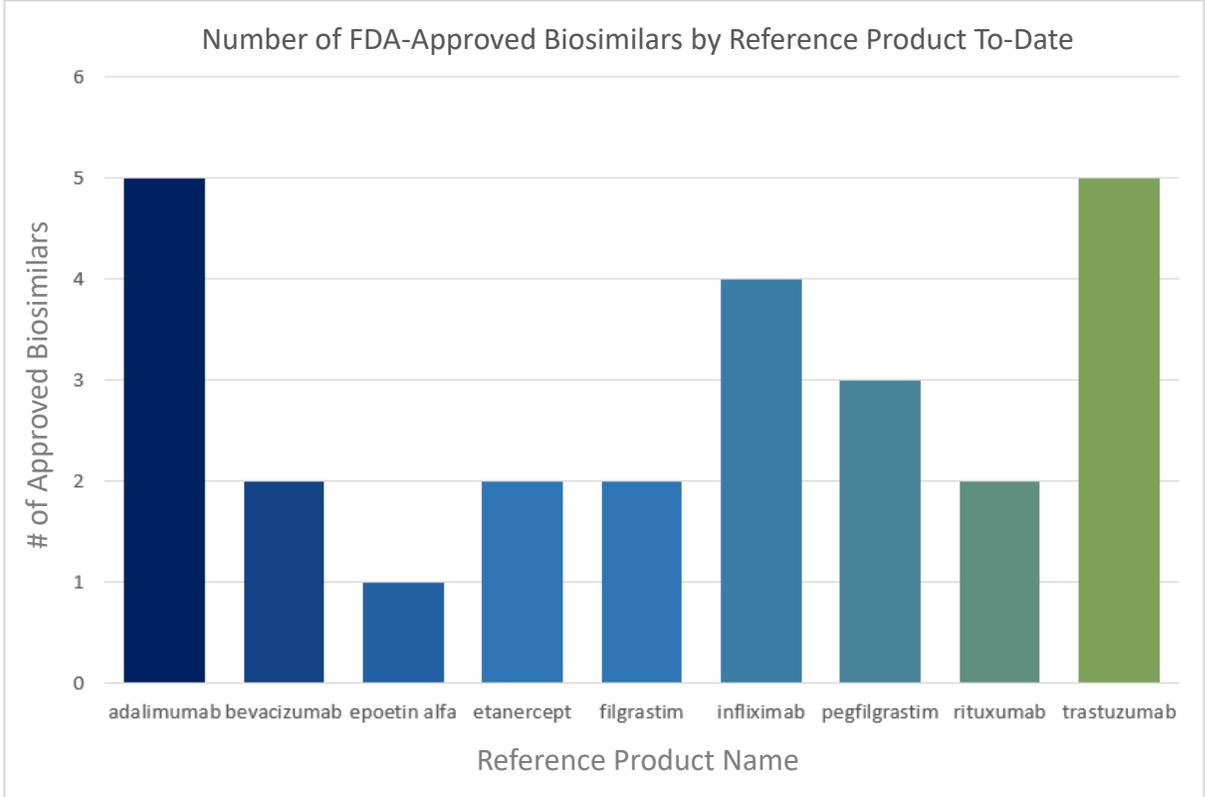
**BIOSIMILARS ACTION PLAN:**  
Balancing Innovation  
and Competition

July 2018

# Biosimilars: 2019 Year in Review



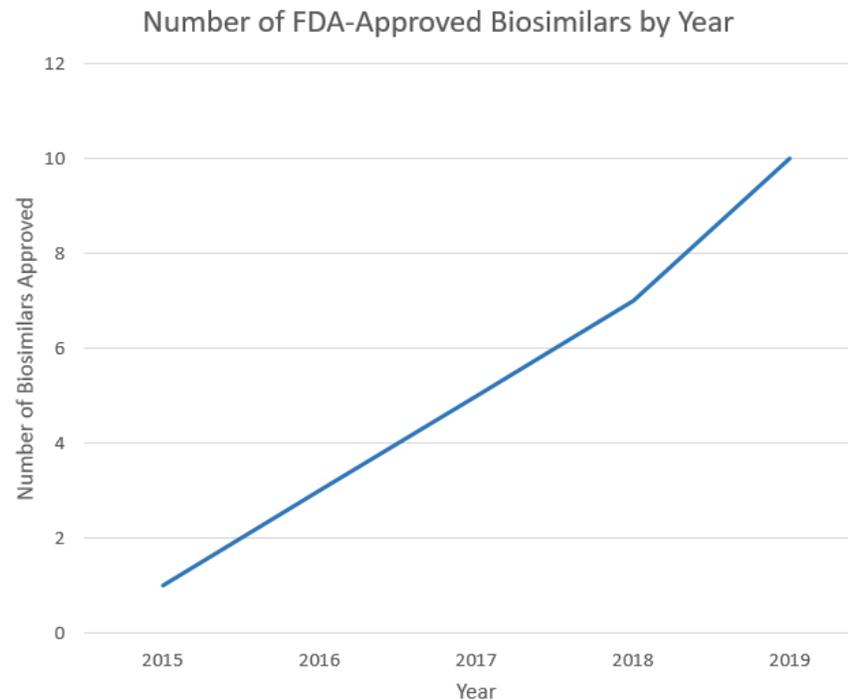
| Biosimilars Approved by FDA in 2019 |                                       |
|-------------------------------------|---------------------------------------|
| <b>Ontruzant</b> (trastuzumab-dttb) | <b>Ruxience</b> (rituximab-pvvr)      |
| <b>Trazimera</b> (trastuzumab-qyyp) | <b>Hadlima</b> (adalimumab-bwwd)      |
| <b>Eticovo</b> (etanercept-ykro)    | <b>Ziextenzo</b> (pegfilgrastim-bmez) |
| <b>Kanjinti</b> (trastuzumab-anns)  | <b>Abrilada</b> (adalimumab-afzb)     |
| <b>Zirabev</b> (bevacizumab-bvzr)   | <b>Avsola</b> (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.)



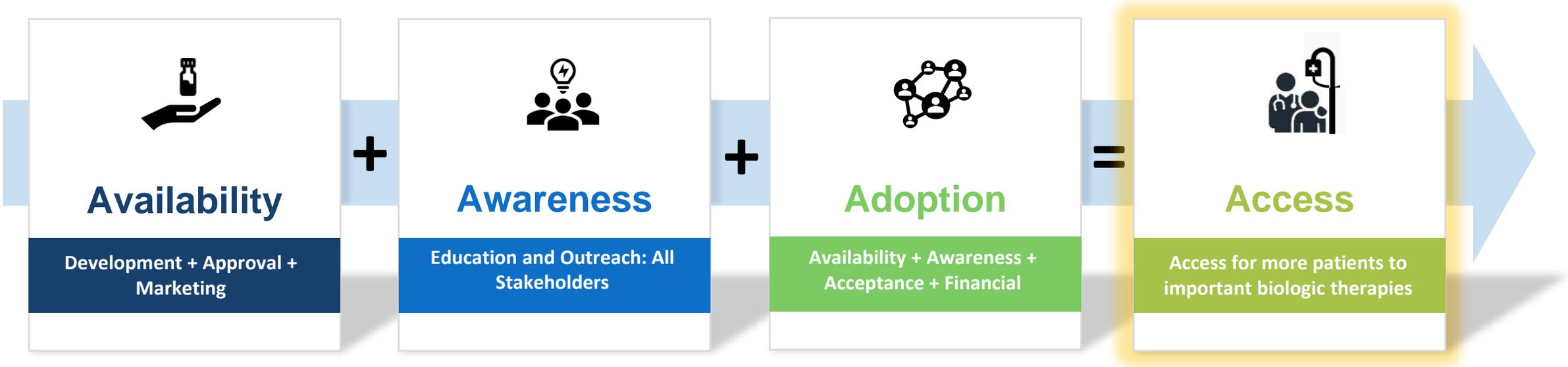
## Completed Activities

## Key In-Progress Activities

|   |   |  |  |  |
|---|---|--|--|--|
| <p>Established the Office of Therapeutic Biologics and Biosimilars</p>  | <p>Released Draft Guidances:</p> <ul style="list-style-type: none"> <li>- "Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations"</li> <li>- "Nonproprietary Naming of Biological Products: Update"</li> <li>- "Clinical Immunogenicity of Biosimilar and Interchangeable Insulin Products"</li> </ul> <p>Released Final Guidance:</p> <ul style="list-style-type: none"> <li>- "Considerations in Demonstrating Interchangeability with a Reference Product"</li> </ul> | <p>Released "Biosimilar Basics" for patients</p> | <p>Enhance the Purple Book</p>   | <p>Develop standardized review templates specific to 351(k) BLAs</p> |
| <p>Published article on "Advancing biosimilar development using Pharmacodynamic (PD) Biomarkers in Clinical Pharmacology Studies"</p> |   | <p>Stakeholder Meetings</p>                      | <p>Provide product developers with information resources and development tools</p> | <p>Identify and develop additional guidances</p>                     |
| <p>Held Public Hearing on "The Future of Insulin Biosimilars"</p>   |   | <p>Other Engagement Activities</p>               | <p>Develop additional biosimilars educational resources</p>                        | <p>Oversee the transition of biological products</p>                 |

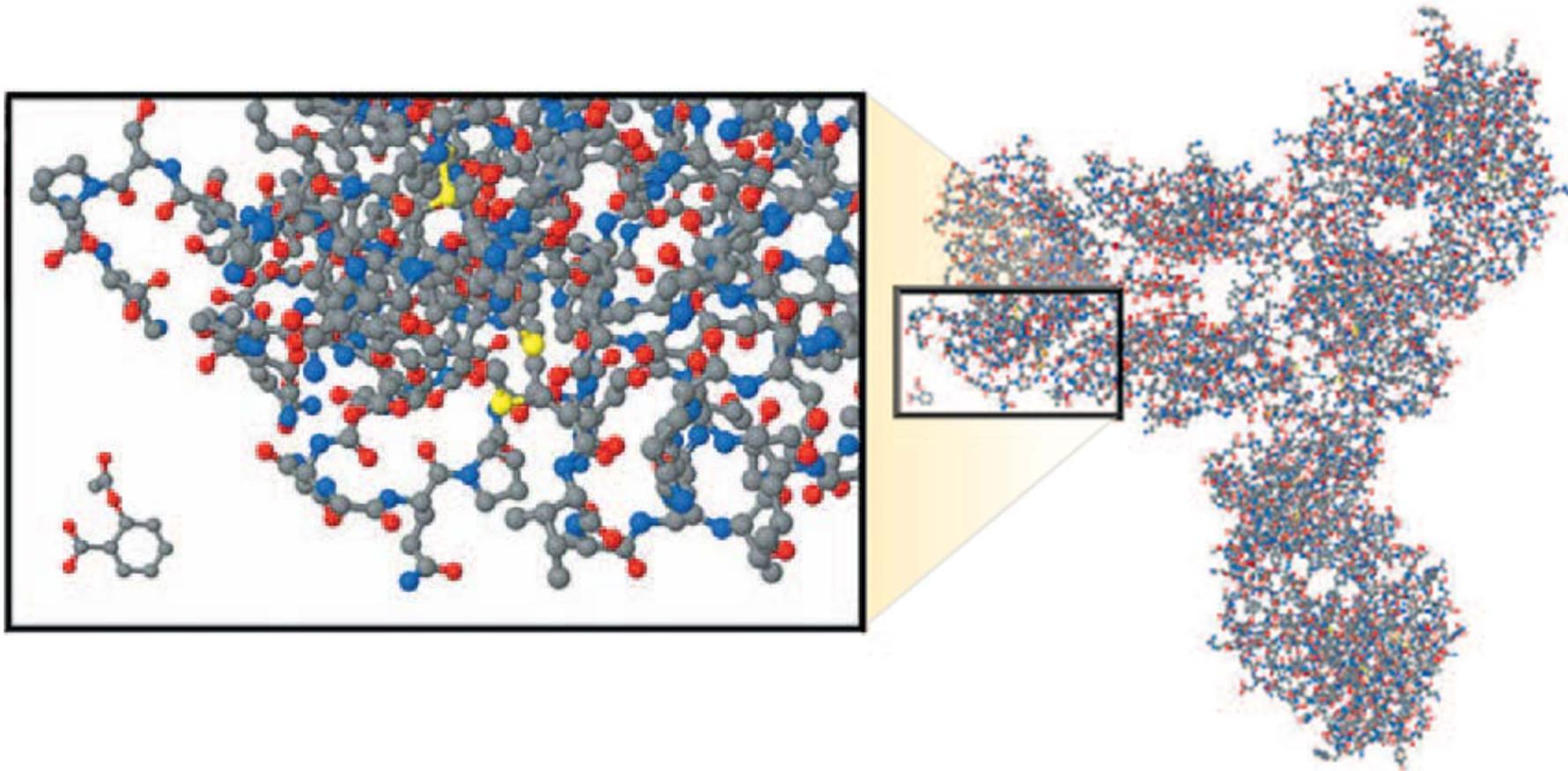


# Solving The Equation for Patient Access

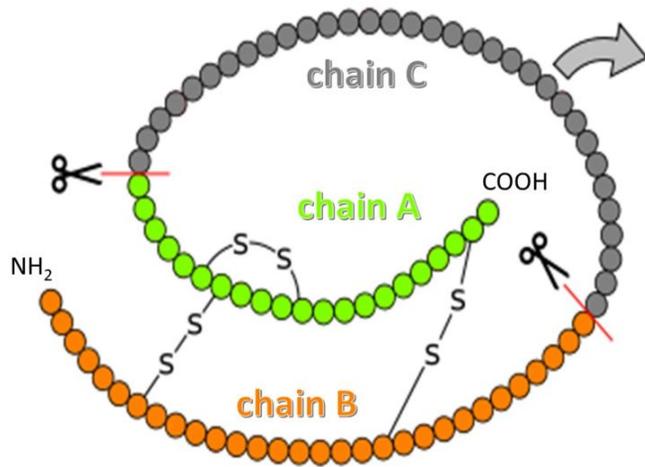


# Introduction to Biosimilarity Concepts

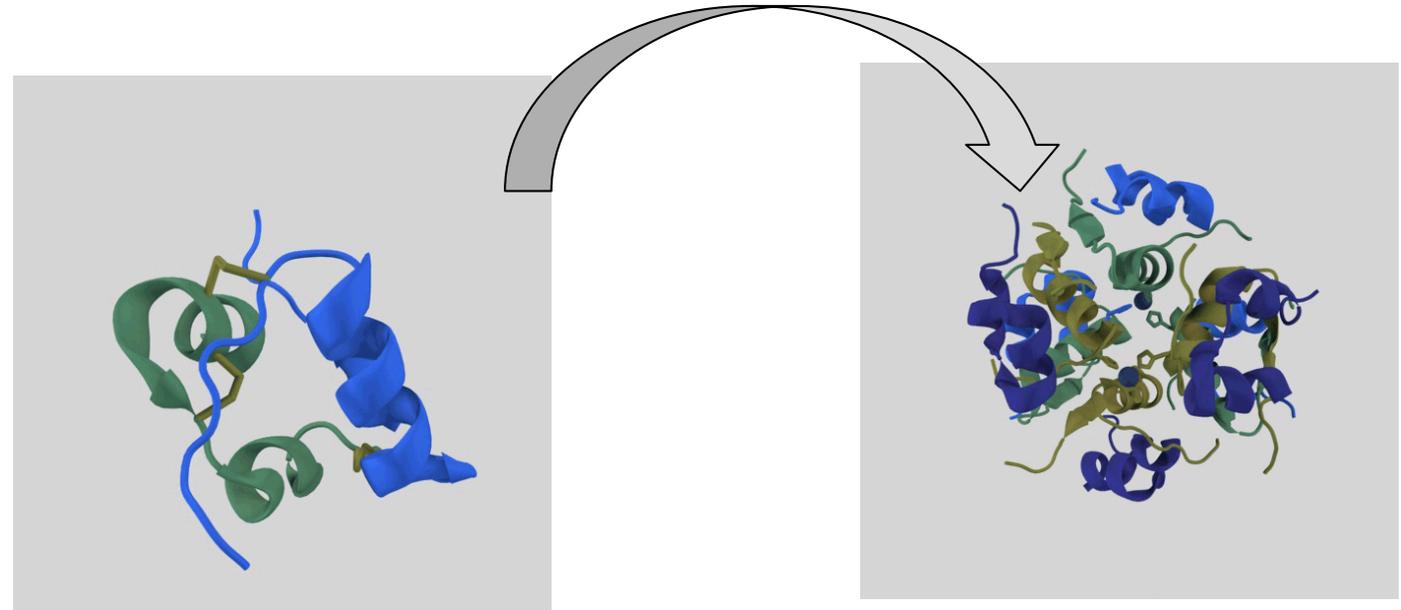
# Biologics vs. Small Molecules



# The Spectrum of Biologic Complexity: Insulin



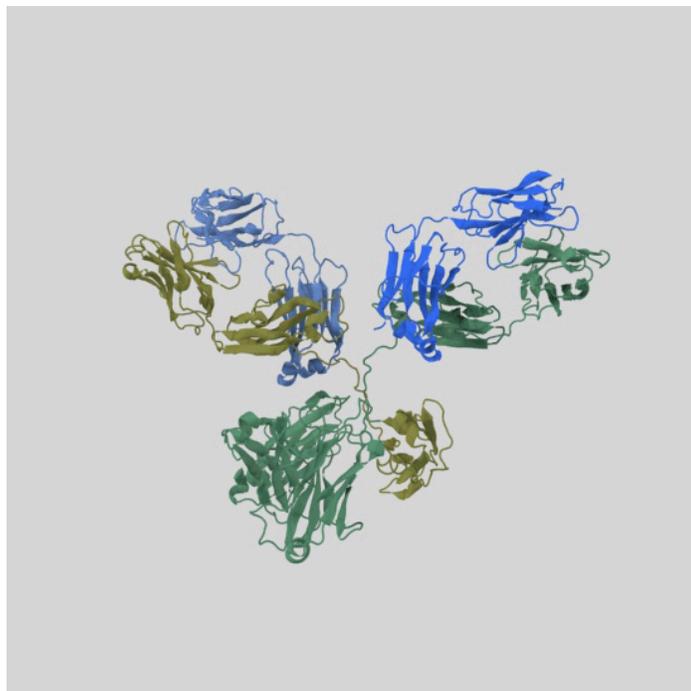
Pro-Insulin  
Chain A = Green;  
Chain B = Orange  
S-S = disulfide bridges



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

Structure: Simple  
Complexity: tendency to aggregate  
and immunogenicity

# The Spectrum of Biologic Complexity: mAbs



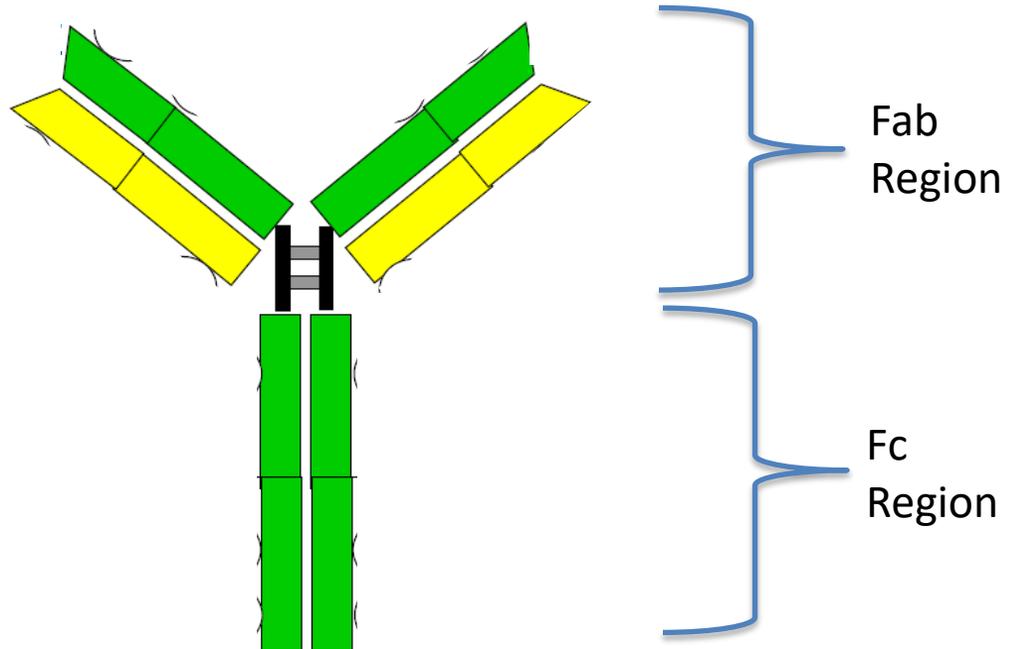
Monoclonal Antibodies  
Heavy Chain x 2 = 50 kDa  
Light Chain x 2 = 25 kDa  
Total Molecular Weight  $\approx$  150 kDa

- 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



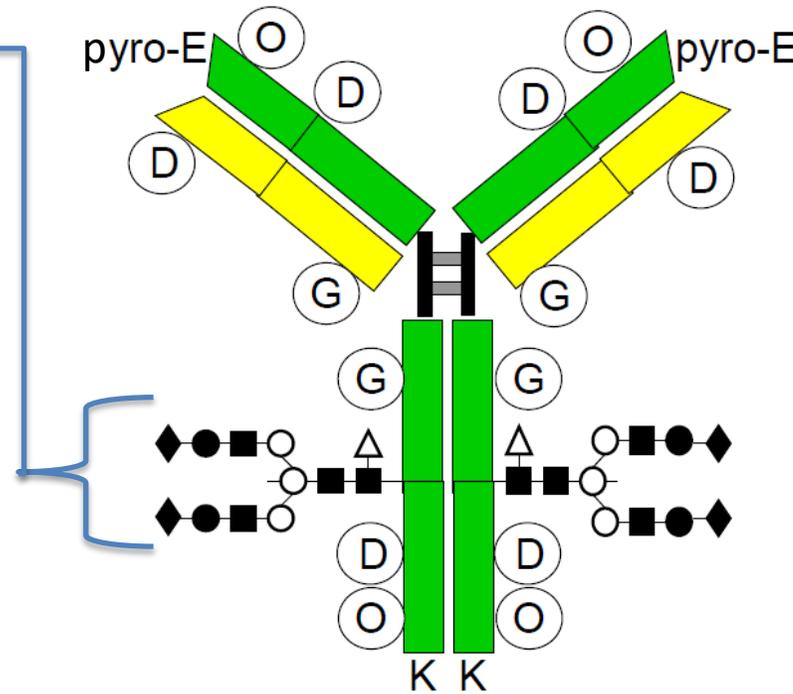
- Biosimilars and the original biologics they are referencing will have the same underlying amino acids and proteins
- So why can't they all be called "identical" or "copies"?
- "Add-ons" and modifications to certain amino acids



# 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



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

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)

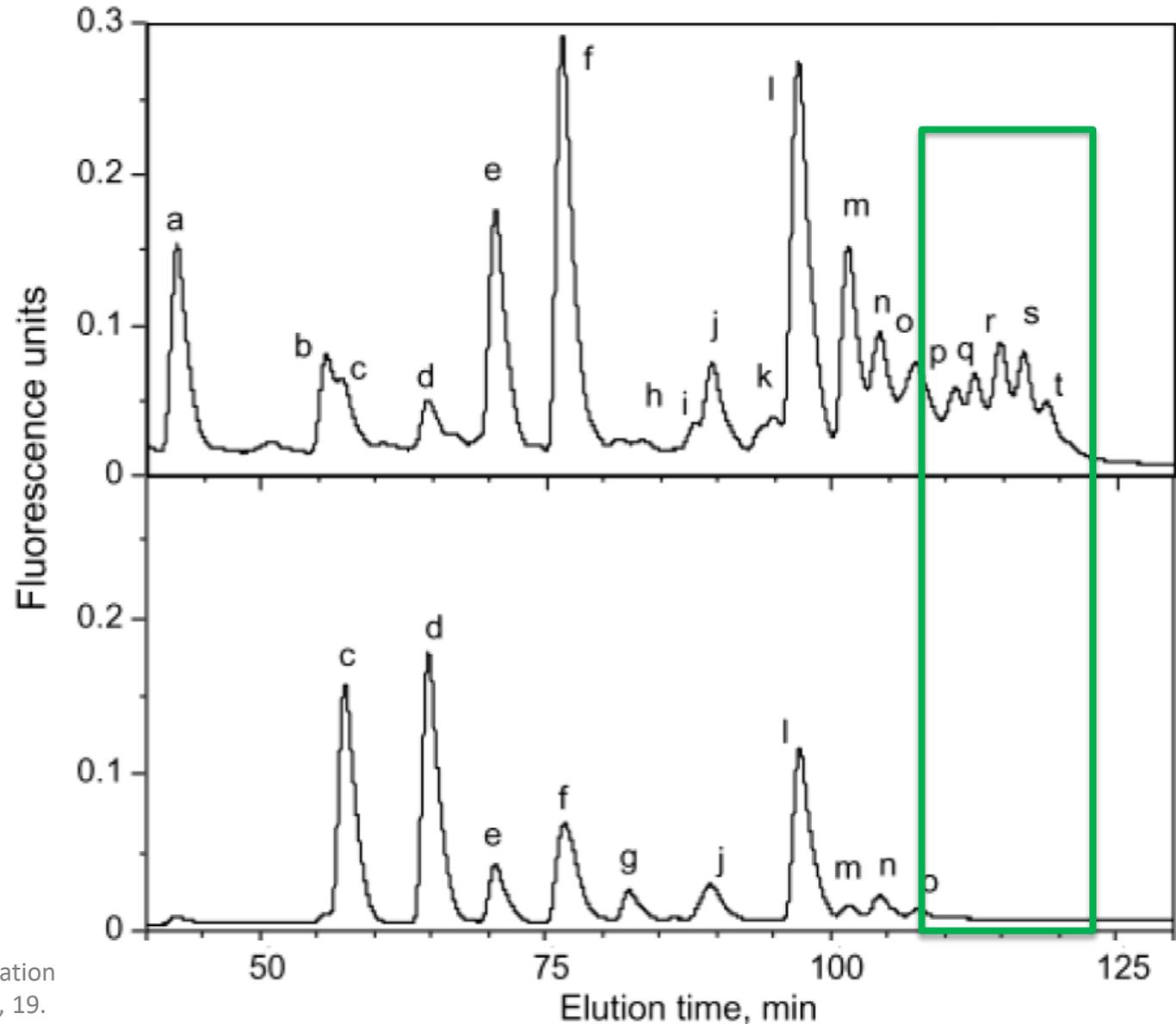
C-terms Lys (2)

$2 \times 6 \times 4 \times 4 \times 5 \times 5 \times 2 = 9600$

# 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?

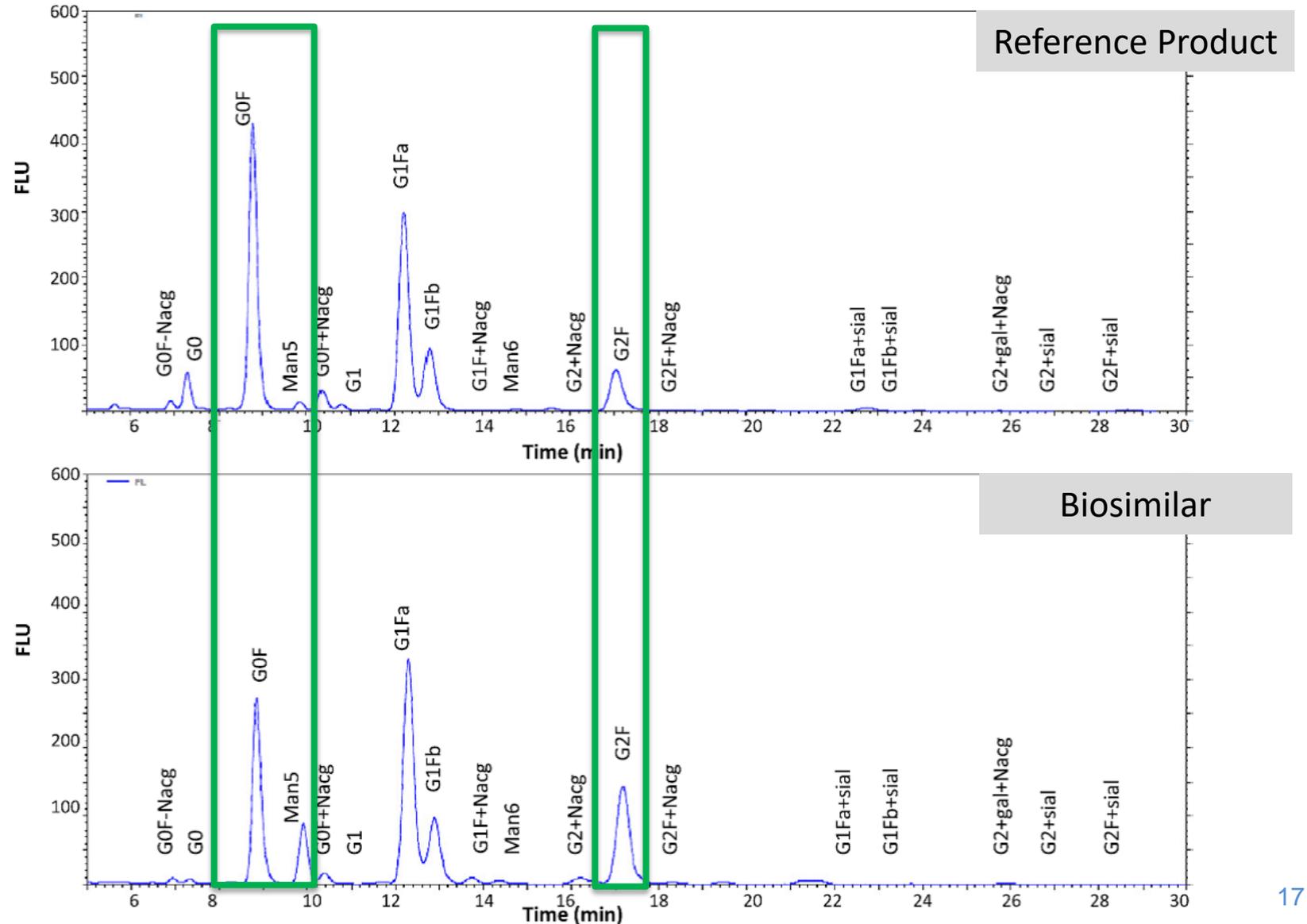


\*These graphs are for illustration purposes only and were not from pharmaceutical samples.

# 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



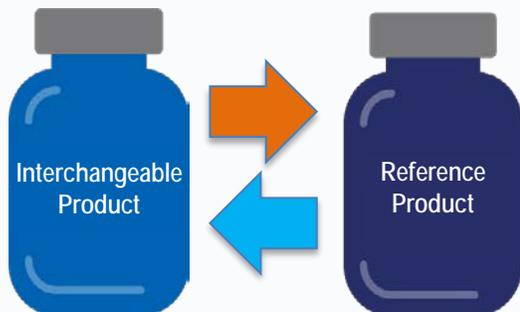
## Reference Product

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

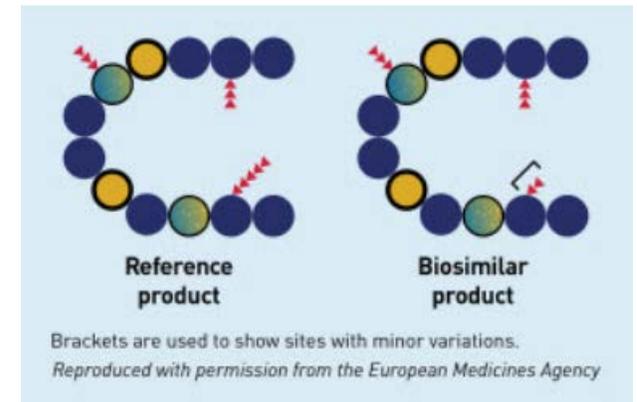


## Interchangeable Product

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)

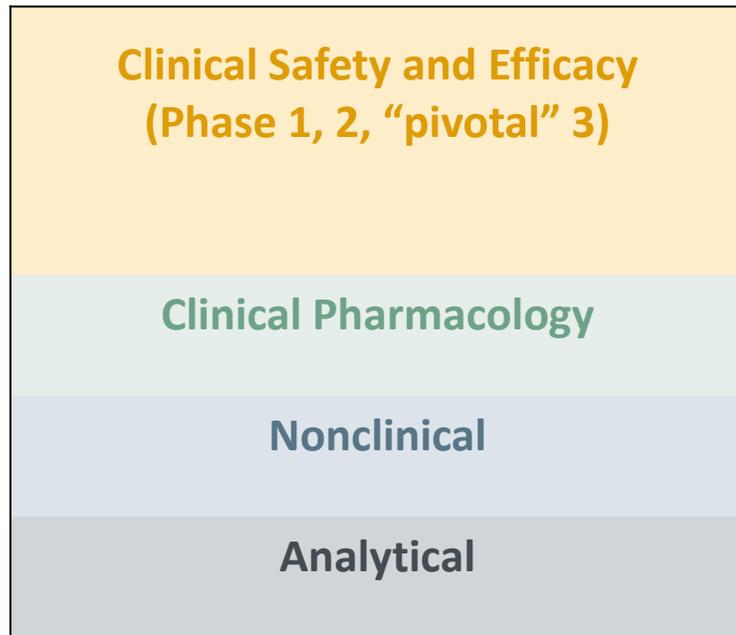
# FDA's Approach to the Development of Biosimilars

# Different Goals for “Stand-alone” vs. Biosimilar Development



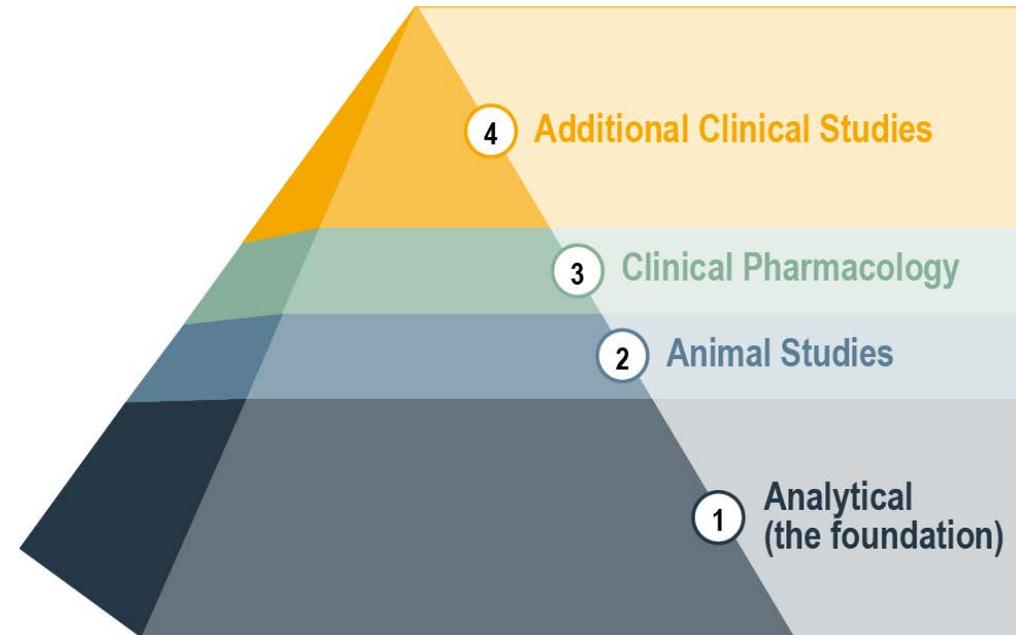
## “Stand-alone”: 351(a) BLA

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

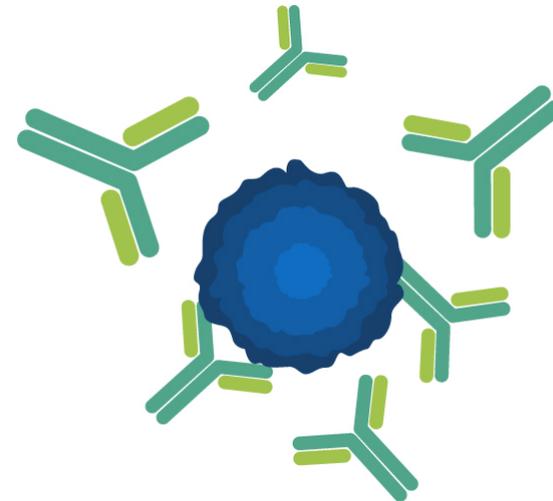
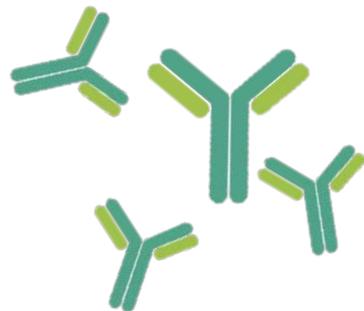


What does this difference mean from a development perspective?

# Immunogenicity

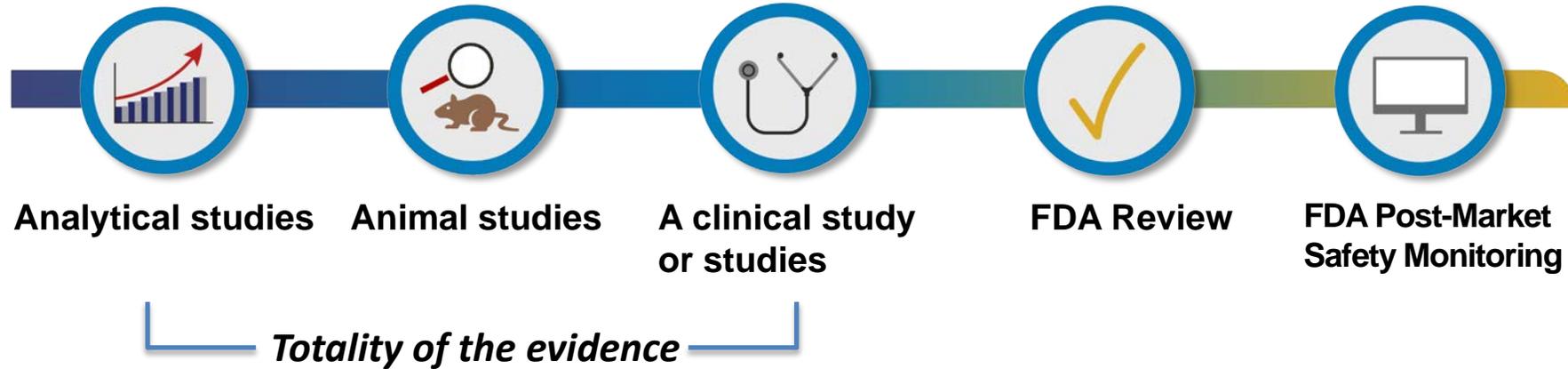


- Immunogenicity refers to the potential for the body to elicit an immune reaction in response to a biological product, which, in rare cases, may result in decreased efficacy of the product
- Biological products, including both reference products and biosimilar products, have a small risk of immunogenic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

# 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.

**Biosimilar & Original Biologic**

- ✓ Same benefits
- ✓ Same potential side effects
- ✓ Same strength and dosage
- ✓ Given the same way

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

The infographic features a smartphone-like frame on the left containing a list of four checked items. To the right, a text box explains that biosimilars use the same natural sources as the original biologics and provide the same treatment benefits. The text "provide the same treatment benefits" is highlighted in a red box.

# 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](mailto: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.

# Resources for Health Care Providers

# Purple Book



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



Home / Drugs / Development & Approval Process | Drugs / How Drugs are Developed and Approved / Types of Applications / Therapeutic Biologics Applications (BLA) / Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations

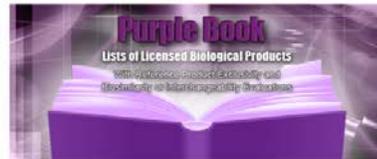
## Purple Book: Lists of Licensed Biological Products with Reference Product Exclusivity and Biosimilarity or Interchangeability Evaluations

Share Tweet LinkedIn Email Print

Therapeutic Biologics Applications (BLA)

Biosimilars

The "Purple Book" lists biological products, including any biosimilar and interchangeable biological products, licensed by FDA under the Public Health Service Act (the PHS Act).



The Purple Book includes the date a biological product was licensed under 351(a) of the PHS Act and whether FDA evaluated the biological product for reference product exclusivity under section 351(k)(7) of the PHS Act.

The Purple Book, in addition to the date licensed, also includes whether a biological product licensed under section 351(k) of the PHS Act has been determined by FDA to be biosimilar to or interchangeable with a reference biological product (an already-licensed FDA biological product). The Patient Protection and Affordable Care Act (Affordable Care

Content current as of: 11/18/2019

- CDER List of Licensed Biological Products (PDF - 217 KB) Updated: 4/21/2019
- CDER List of Licensed Biological Products (PDF - 140 KB) Updated: 11/18/2019
- More Information on the Lists

Back to Top

Center for Biologics Evaluation and Research  
List of Licensed Biological Products with (1) Reference Product Exclusivity and (2) Biosimilarity or Interchangeability Evaluations to Date

| BLA STN | PRODUCT (PROPE) NAME   | PROPRIETARY NAME   | DATE OF LICENSURE (mo/day/yr) | DATE OF FIRST LICENSURE (mo/day/yr) | REFERENCE PRODUCT EXCLUSIVITY EXPIRE DATE (mo/day/yr) | INTERCHANGEABLE/BIOSIMILAR (B) | WITHDRAWN |
|---------|--|--|-------------------------------|-------------------------------------|---|--------------------------------|-----------|
| 125296  | Adenovirus Type 4 and Type 7 Vaccine, Live, Oral                                     |  | 01/12/2011                    |                                     |   |                                |           |
| 102138  | Albumin (Human)  | Plasbumin-5, Plasbumin-20, Plasbumin-25, Albumin             | 00/01/1942                    | NA                                  | NA  |                                |           |
| 102452  | Albumin (Human)  | Buminate, Buminate 25N, Buminate 5N, Buminate 10N, Plasbumin | 3/3/1954                      | NA                                  | NA  |                                |           |
| 102893  | Albumin (Human)  |  | 9/7/1975                      | NA                                  | NA  |                                |           |
| 102265  | Albumin (Human)  | Albumin  | 10/1/1975                     | NA                                  | NA  |                                |           |
| 102476  | Albumin (Human)  | Albumin  | 9/15/1976                     | NA                                  | NA  |                                |           |
| 102892  | Albumin (Human)  | Albumin; Albumin-C; Albumin-20; Albumin-25                   | 3/17/1985                     | NA                                  | NA  |                                |           |
| 102895  | Albumin (Human)  |  | 5/17/1989                     | NA                                  | NA  |                                |           |
| 125154  | Albumin (Human)  |  | 10/17/2006                    | NA                                  | NA  |                                |           |
| 125384  | Albumin (Human)  | Infbumin   | 6/29/2011                     |                                     |   |                                |           |
| 125444  | Albumin (Human) Alpha Allergen: Cultural Keratins and Fibronectin in Bovine Collagen | ALBUMIND   | 6/19/2018                     |                                     |   |                                |           |
| 125400  |  | IGATU1   | 3/9/2012                      |                                     |   |                                |           |
| 102174  | Alpha-2-Proteinase Inhibitor (Human)   | Protasol; Protasol-C   | 12/12/1987                    | NA                                  | NA  |                                |           |
| 125208  | Alpha-2-Proteinase Inhibitor (Human)   | Protasol; Protasol NP  | 12/12/2002                    | NA                                  | NA  |                                |           |
| 125278  | Alpha-2-Proteinase Inhibitor (Human)   | Zemana   | 1/8/2005                      | NA                                  | NA  |                                |           |
| 125225  | Alpha-2-Proteinase Inhibitor (Human)   | Alphas   | 7/12/2010                     |                                     |   |                                |           |
| 102824  | Animal Allergens, Standardized Cat Hair  |  | 7/11/1983                     | NA                                  | NA  |                                |           |
| 102868  | Animal Allergens, Standardized Cat Hair  |  | 9/12/1974                     | NA                                  | NA  |                                |           |
| 102897  | Animal Allergens, Standardized Cat Hair  |  | 9/12/1988                     | NA                                  | NA  |                                |           |
| 102872  | Animal Allergens, Standardized Cat Hair  |  | 9/12/1974                     | NA                                  | NA  |                                |           |
| 102865  | Animal Allergens, Standardized Cat Hair  |  | 11/19/1971                    | NA                                  | NA  |                                |           |
| 102889  | Animal Allergens, Standardized Cat Hair  |  | 9/12/1988                     | NA                                  | NA  |                                |           |
| 102961  | Animal Allergens, Standardized Cat Hair  |  | 9/12/1982                     | NA                                  | NA  |                                |           |
| 102890  | Animal Allergens, Standardized Cat Hair  |  | 3/13/1983                     | NA                                  | NA  |                                |           |
| 125162  | Antihemophilic Globulin (Human)  | Antihem  | 10/12/2015                    |                                     |   |                                |           |
| 102821  | Anti-toxin Vaccine (Adults)  | Bot/Tetax  | 11/2/1975                     | NA                                  | NA  |                                |           |
| 102180  | Anti-thrombin Factor (Human)   | Kealte; Kealte-Del   | 11/9/1974                     | NA                                  | NA  |                                |           |
| 102448  | Anti-thrombin Factor (Human)   | KealteTM   | 9/11/1994                     | NA                                  | NA  |                                |           |
| 102863  | Anti-thrombin Factor (Human)   | Monoclonal-P; Monoclonal                                     | 9/18/1973                     | NA                                  | NA  |                                |           |
| 102832  | Anti-thrombin Factor (Recombinant)   | Kogenate; Malsate PL; Kogenate PL                            | 3/25/1993                     | NA                                  | NA  |                                |           |
| 102875  | Anti-thrombin Factor (Recombinant)   | Recombinant; Bectra (Human)                                  | 11/19/1993                    | NA                                  | NA  |                                |           |
| 102878  | Anti-thrombin Factor (Recombinant)   | ReFacto  | 3/6/2000                      | NA                                  | NA  |                                |           |
| 125466  | Anti-thrombin Factor (Recombinant)   | Kealtegen  | 10/11/2013                    |                                     |   |                                |           |
| 125487  | Anti-thrombin Factor (Recombinant), 0.1 human protein                                | GLTACTE  | 6/26/2014                     |                                     |   |                                |           |
| 125274  | Anti-thrombin Factor (Recombinant), Full Length                                      | EDNATSE  | 3/16/2014                     |                                     |   |                                |           |
| 125471  | Anti-thrombin Factor (Recombinant), Glucosylated, av...                              | SPINACT  | 3/19/2010                     |                                     |   |                                |           |
| 125264  | Anti-thrombin Factor (Recombinant), HCl salt   | ADPHACTE   | 11/12/2015                    |                                     |   |                                |           |
| 125261  | Anti-thrombin Factor (Recombinant), HCl salt, acid                                   | Act  | 6/26/2014                     |                                     |   |                                |           |
| 125264  | Anti-thrombin Factor (Recombinant), Human/Albunin One                                | SPINACT; SPINACT SOLUTION                                    | 3/12/2010                     |                                     |   |                                |           |
| 125263  | Anti-thrombin Factor (Recombinant), Human/Albunin One Method                         | Activo   | 10/2/2003                     | NA                                  | NA  |                                |           |

## 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



# 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](http://www.fda.gov/biosimilars)



# 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



**Biosimilar Basics**

Biosimilars are safe and effective biologic medications for treating many illnesses such as chronic skin and bowel diseases, arthritis, kidney conditions and cancer.

Biologic medications are generally made from **natural sources** and developed using advanced science. Biosimilars are **FDA-approved** medications that are compared to another medication — the original biologic.

Biosimilars are made with the same type of natural source as the original biologic they were compared to — and **provide the same treatment benefits.**

**Benefits:**

- More access to important treatments.
- More competition in the health care market.
- Lower costs.

Biosimilars are approved by FDA after a **careful review** of data, studies, and tests. FDA monitors the **safety** and **effectiveness** of all medications after their approval.

Check for medication quality during production. Report problem using reports.

Visit [www.FDA.gov/biosimilars](http://www.FDA.gov/biosimilars) and talk with your doctor to learn more.

FDA U.S. FOOD & DRUG ADMINISTRATION

# 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](http://www.fda.gov/biosimilars) for access to all the education materials and information about biosimilar and interchangeable products
- Visit the [www.fda.gov/purplebook](http://www.fda.gov/purplebook) for information on biological products, including if products are biosimilar to a reference product
- Visit [www.fda.gov/drugsatfda](http://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](http://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval)
2. Purple Book: [www.fda.gov/purplebook](http://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
4. Liu L, "Antibody glycosylation and its impact on the pharmacokinetics and pharmacodynamics of monoclonal antibodies and Fc-fusion proteins." *J Pharm Sci* 2015, 104:1866-1884
5. Hmiel LK, Brorson KA, Boyne MT, "Post-translational structural modifications of immunoglobulin G and their effect on biological activity." *Anal Bioanal Chem* 2015, 407:79-94
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](http://www.fda.gov/biosimilars)

