FDA Drug Topics:

Biosimilars: A Review of Scientific, Regulatory, and Clinical Considerations for Health Care Providers

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FDA Approved Biosimilar and Interchangeable Products*

Product Class		Approvals
Supportive Care	Filgrastim	B B B
	Epoetin	B
	Pegfilgrastim	B B B B B B
Oncology	Rituximab	B B B
	Bevacizumab	B B B B
	Trastuzumab	B B B B B
Autoimmune	Infliximab	B B B B
	Etanercept	B B
	Adalimumab	B I B B B B B B B
	Insulin Glargine	I I
Ophthalmology	Ranibizumab	B I

B Biosimilar

I Interchangeable Biosimilar

- **41 Biosimilars Approved**
- **29 Currently marketed**

*as of May 31, 2023

Learning Objectives

1. Review the key definitions, nomenclature, labeling, issues of interchangeability, and similarities and differences between biosimilars and reference biologics.

2. Describe how biologics differ from small molecules (size, complexity, inherent variation) and compare the biosimilar and generic approval pathways.

3. Explain the statutory requirements and approval process for biosimilars and interchangeables.

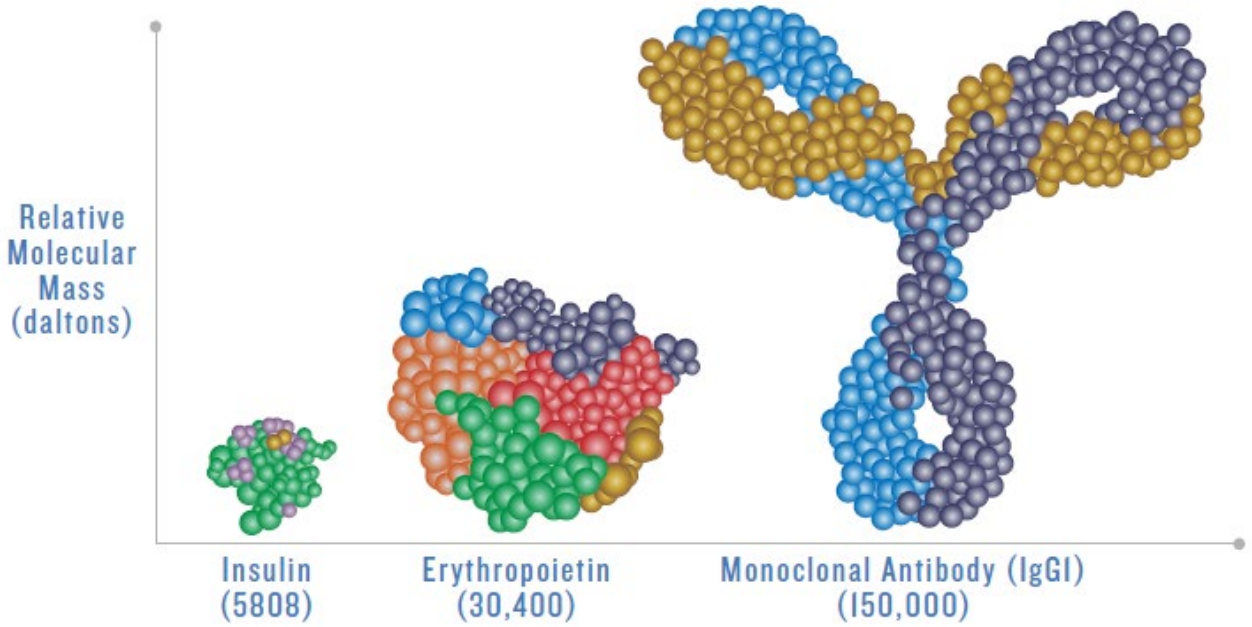
4. Discuss considerations for prescribing and dispensing biosimilars and interchangeable biosimilars.

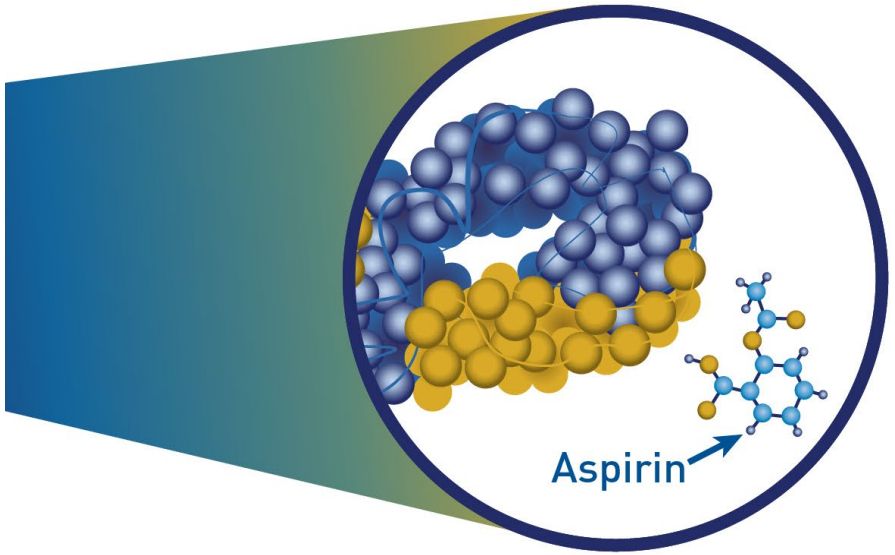
5. Summarize the new resources available for health care providers and faculty to learn more about biosimilar and interchangeable products and how to use the Purple Book Database of Licensed Biological Products.

Biosimilar and Interchangeable Products: Scientific Concepts and Regulatory Framework

Biological Products

- Biologics are generally large and produced from living systems
- They range in size and complexity
- Examples: therapeutic proteins (hormones, growth factors, monoclonal antibodies), vaccines, blood products

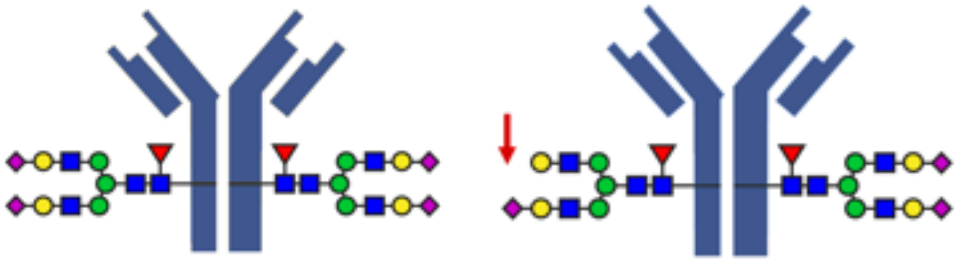




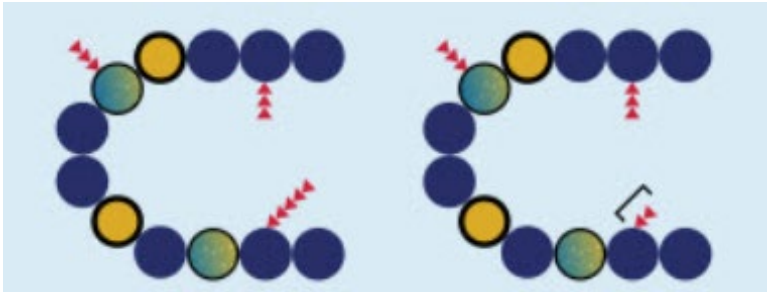
Modified from Mellstedt H, EJC Supplements II, 2013, 3, I - II

Therapeutic Proteins: Complexity

- Cells can make exact copies of a protein but other add-ons and changes may occur, resulting in different versions of the molecule (inherent variation)



- Millions of slightly different versions of the same protein or antibody per dose or batch



- Biologics manufacturers try to keep a consistent mix of variants across batches of their products and over time

Biological Product Regulation

- **351(a) "stand alone" Biologics License Application (BLA):** contains all information and data necessary to demonstrate that the proposed biological product is safe, pure and potent

- **The Biologics Price Competition and Innovation Act** of 2009 (BPCI Act)
  - Created an **abbreviated licensure pathway (351(k))** for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product (originator biological product)

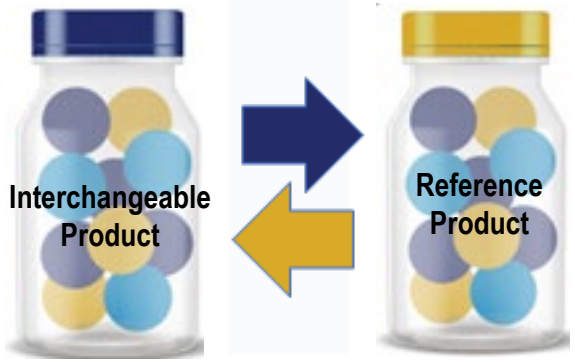
Key Definitions from the BPCI Act

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 to and has no clinically meaningful differences from** an existing FDA-approved reference product



Interchangeable Product

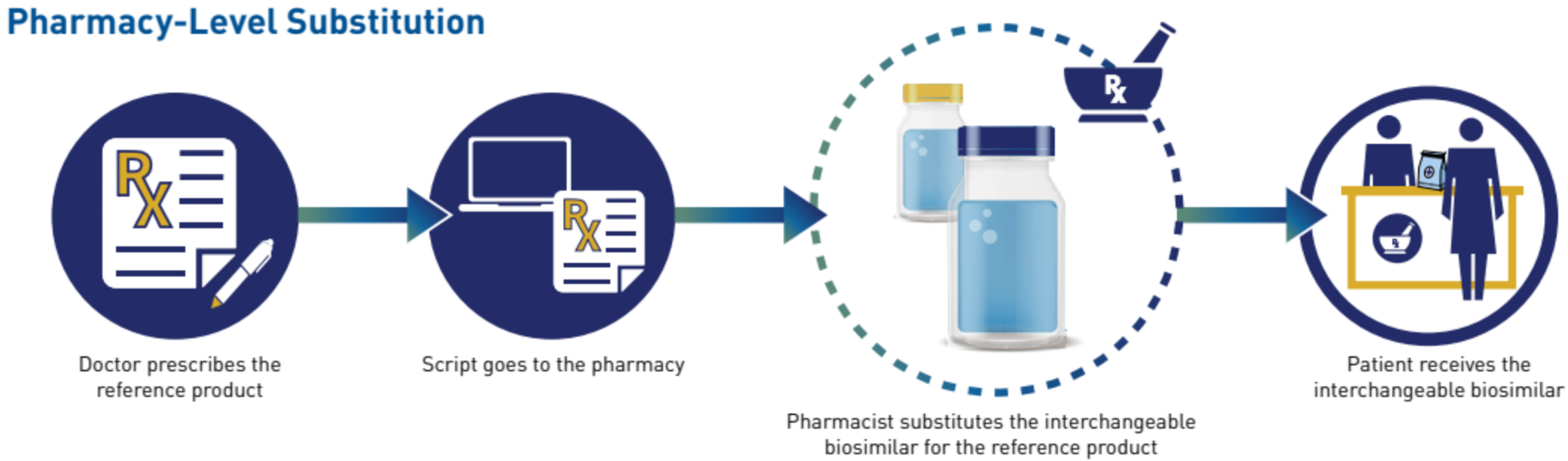
-Is a biosimilar

-Expected to produce the same clinical result as the reference product (RP) in any given patient

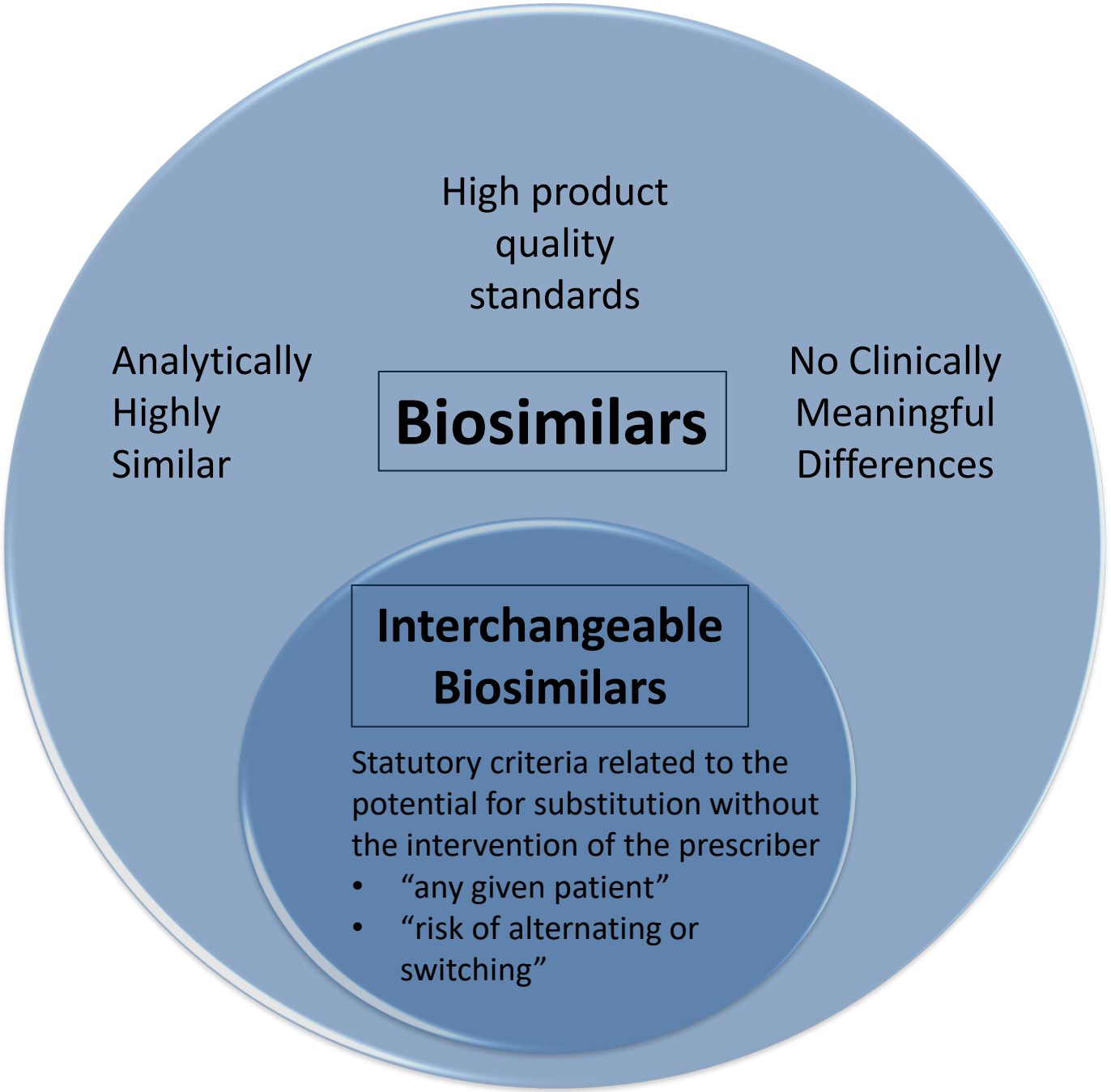
-Switching between the proposed product and the RP does not ↑safety risks or ↓effectiveness compared to using the RP without switching

Why Seek Interchangeability?

An interchangeable biosimilar product can be **substituted for the reference product at pharmacies** without the intervention of the prescribing health care provider, subject to state pharmacy laws.



Biosimilars and Interchangeable Biosimilars



- Applicants request licensure as a biosimilar or interchangeable biosimilar
- An applicant may be first approved as a biosimilar but later seek interchangeability
- The analytical similarity and product quality standards are **the same** for biosimilars and interchangeable biosimilars
- Statutory criteria related to the potential for substitution without the intervention of the prescriber

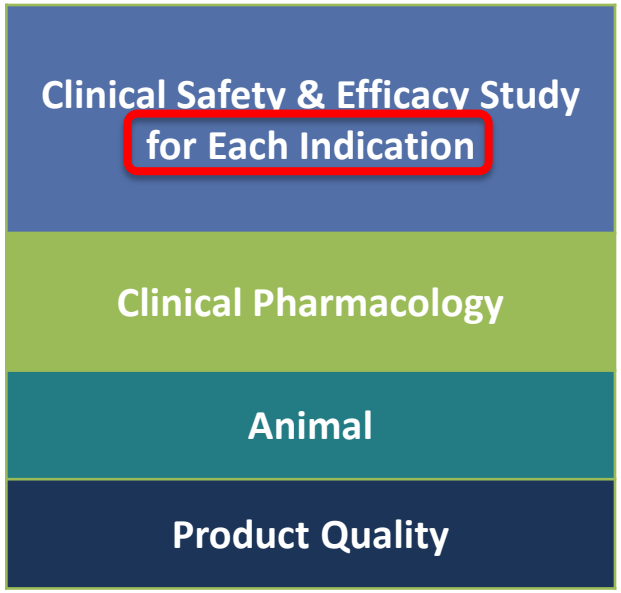
General Requirements

A 351(k) application must include information demonstrating that the biological product:

- Is **biosimilar** to a reference product
  - **Highly similar to and has no clinically meaningful differences from the** FDA-approved 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.**

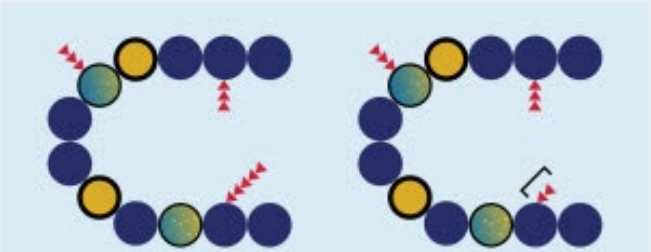
Different Goals for "Stand-alone" vs. Biosimilar Development

"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 based on comparative assessments

Generic vs. Biosimilar

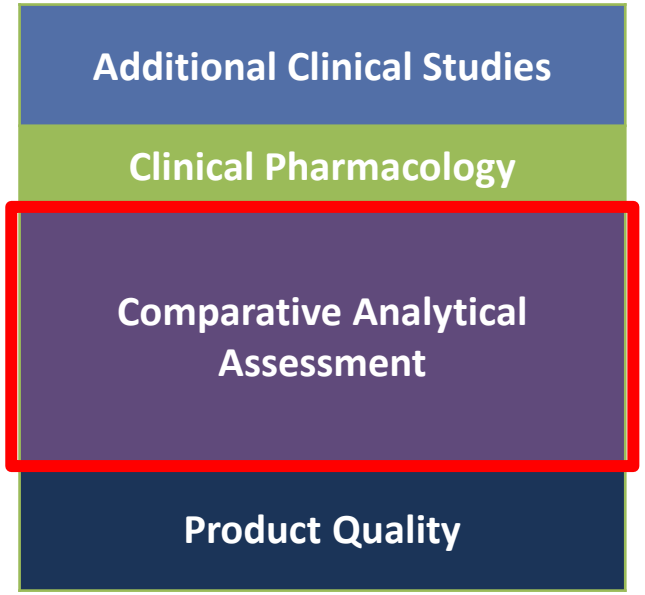
	Generic (Orange Book)	Biosimilar (Purple Book)
Assessment	"Same" Active Ingredient PK Bioequivalence	"Highly Similar" No Clinically Meaningful Differences
Example schematic of product comparisons. Comparative Analytical data expected for both products	 **Reference Listed Drug** **Generic Drug**	
Clinical Pharmacology Studies	Compare PK, when applicable	Compare PK, and PD, when applicable
Other clinical study(ies)	-	Assess immunogenicity; may further evaluate safety and efficacy

Both are "abbreviated" development pathways that have distinct statutory requirements and scientific expectations supporting their approval.

FDA's Recommended Approach to the Development of Biosimilars and Interchangeable Biosimilars

Comparative Analytical Assessment is the Foundation

- Compare multiple physicochemical and biological attributes of each product
  - Analytical studies are generally more **sensitive** than clinical studies in detecting differences between products, should differences exist
  - A biosimilar product with **highly similar structure and function** to the reference product should behave like the reference product
- Analyze multiple lots of the reference product and proposed biosimilar for product quality attributes, including:
  - Primary amino acid sequence
  - Higher order structure (protein folding)
  - Post-translational modifications (glycosylation, etc.)
  - Heterogeneity (charge, size, aggregates, etc.)
  - Biological activity - evaluation of attributes that affect the known MoAs



CAA Example 1: Semglee (insulin glargine-yfgn) vs US-Lantus: Quality Attributes Compared*

Primary structure

- Amino acid sequence and mass

Higher order structure

- Conformation
- Secondary structure
- Tertiary and higher order structures
- Hydrodynamic radius
- Disulfide bonds

Product Variants

- Deamidation
- Glycerol ester
- Citric acid conjugate
- Acetylation

Mitogenic Activity

- IR-A phosphorylation
- Mitogenic assay (Sao2 cells)
- IR-A binding kinetics
- IGF1R binding kinetics

Metabolic Activity

- IR-B phosphorylation
- Glucose uptake assay
- IR long form receptor binding kinetics
- IR autophosphorylation
- Adipogenesis assay
- Inhibition of stimulated lipolysis assay

Protein Concentration

- Activity and concentration in U/mL

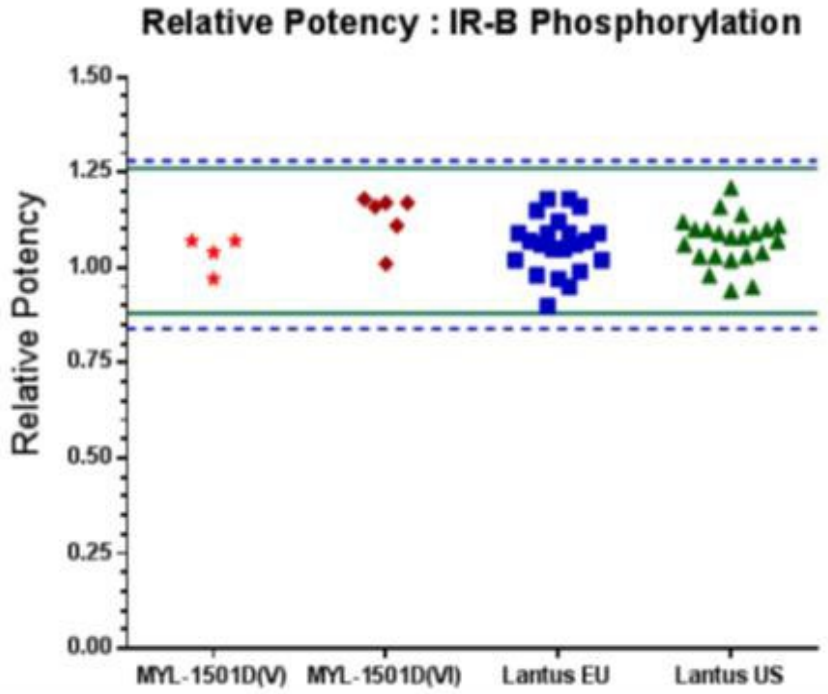
Other

- Zinc content
- Aggregates/High molecular weight proteins
- Isoelectric point

*Not an exhaustive list; Information summarized and adapted from the Product Quality Review available on drugs@fda

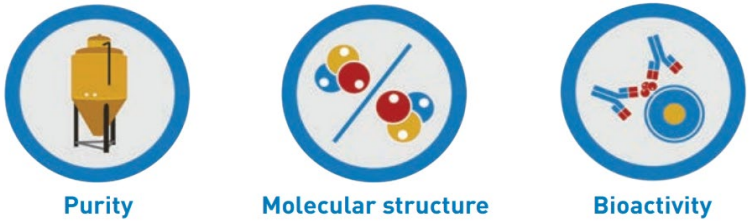
CAA Example 1: Semglee (insulin glargine-yfgn) vs US-Lantus: Insulin Receptor IR-B Phosphorylation

Figure 13: Scatter Plot Distribution for Relative potency (IR-B phosphorylation activity) of MYL-1501D, EU-approved Lantus® and US-approved Lantus®



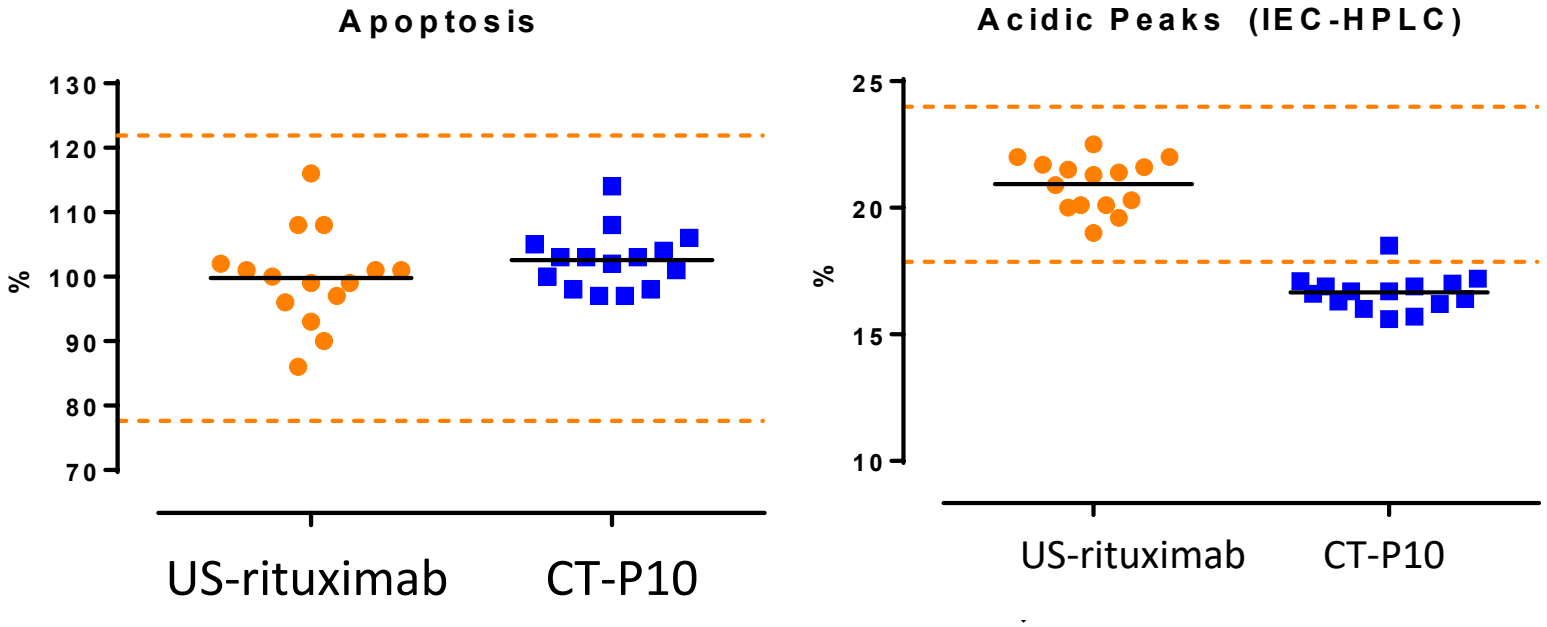
- Green lines represent the quality range (QR) limits (mean ± 3SD of US-Lantus).
- The values of relative IR-B phosphorylation activity for all MYL-1501D lots are 100% within the QR of US-Lantus

These studies provide data to support the physiochemical structural and functional similarity of MYL-1501D to US-Lantus and evaluate the impact of any differences identified.



Adapted from the Product Quality Review available on drugs@fda

CAA Example 2: CT-P10 vs US-Rituximab: Potency and Charge Variants

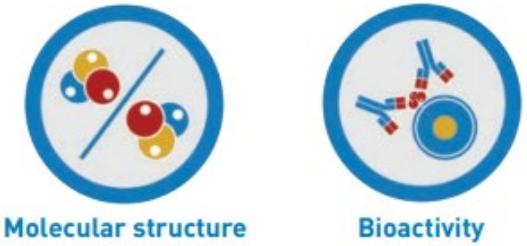


The black bars represent the mean percentages.

The orange lines represent the QR limits (mean ± 3SD of the US-rituximab).

Additional Analytical Studies Showed:

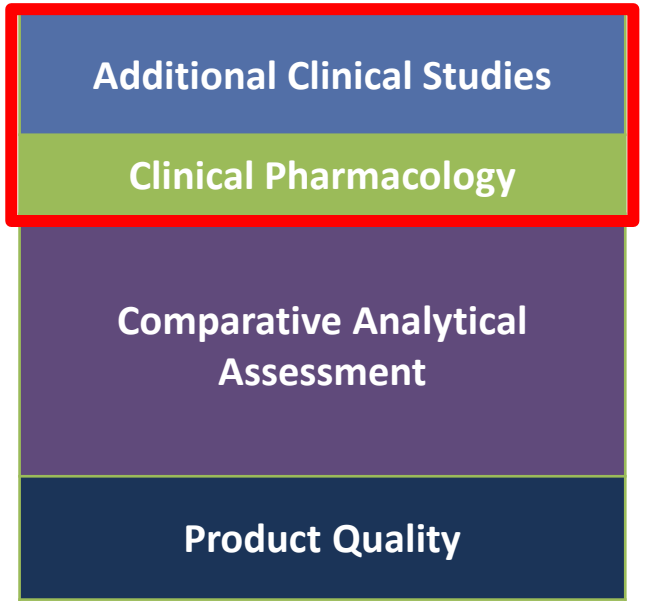
- Charge peaks contain same variants
- Similar biological activity between both products for each peak



Adapted from Oct. 10, 18 FDA ODAC Slides: [Slides from the October 10, 2018 Meeting of the Oncologic Drugs Advisory Committee]

Role of Clinical Studies

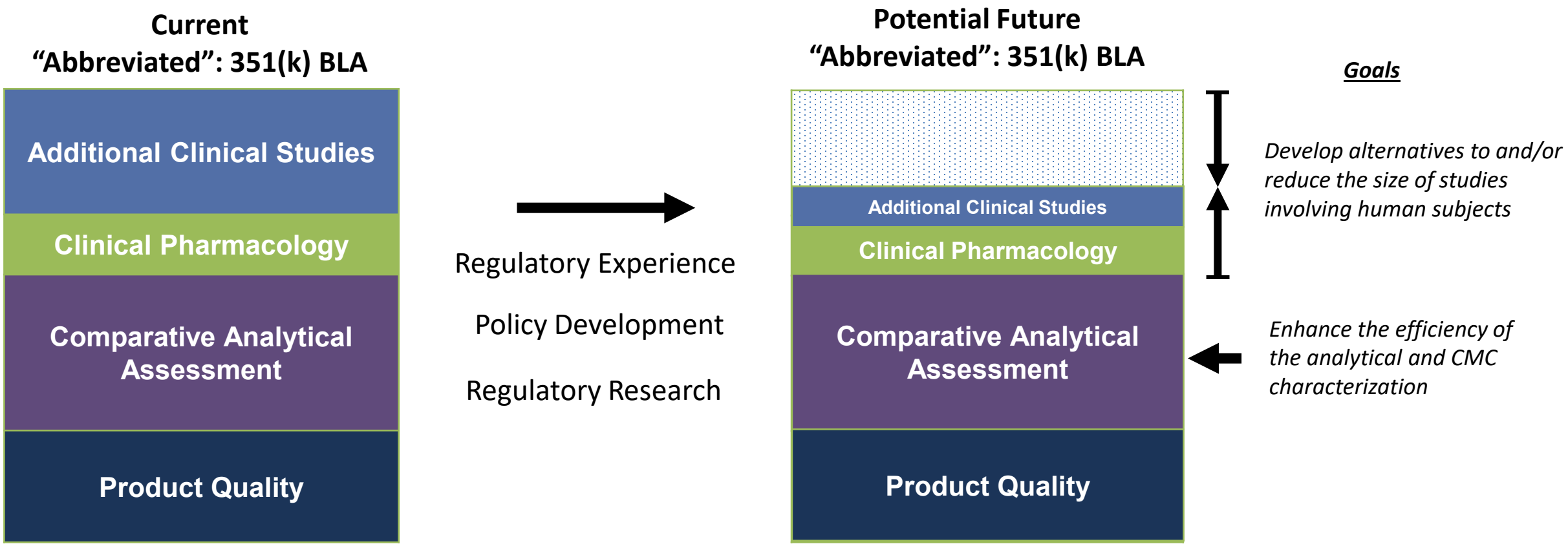
- As a scientific matter, FDA expects an adequate clinical PK, and PD if relevant, comparison between the proposed biosimilar product and reference product and a clinical immunogenicity assessment
- Additional clinical studies are not considered “pivotal” in the way Phase 3 clinical trials are for standalone development
- Add to the totality-of-the-evidence that supports a demonstration of biosimilarity



Type of Clinical Data

- Clinical Pharmacology Studies
  - **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 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)
  - Use of **a single scientifically appropriate PD biomarker or a composite of more than one** relevant PD biomarker to demonstrate PD similarity can reduce residual uncertainty.
- At least 1 clinical study that includes a comparison of the **immunogenicity** of the proposed and reference product generally will be expected
- A **comparative clinical study that compares safety and efficacy in patients** is currently expected if there are **residual uncertainties** about whether there are **clinically meaningful differences** between the proposed and reference products based on structural and functional characterization, human PK and PD data, and clinical immunogenicity assessment.

Focused Efforts to Streamline Biosimilar Development



Clinical Program Example 1: Semglee (insulin glargine-yfgn) vs US-Lantus PK/PD Compared

Figure 2. Mean plasma M1 concentration versus time profiles by treatment in Study MYL-1501D-1003

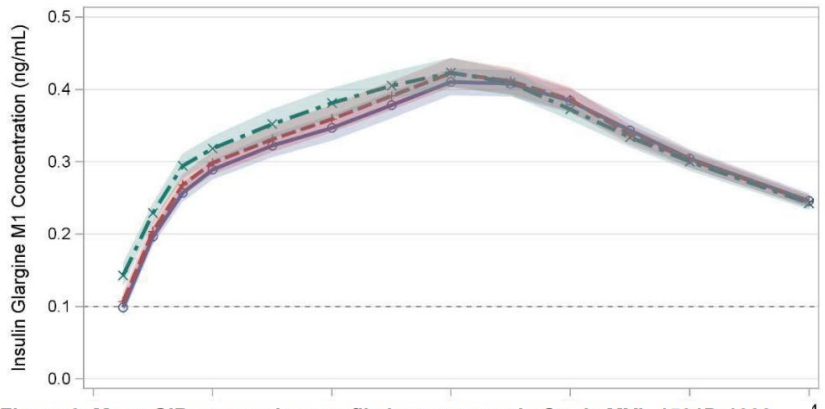
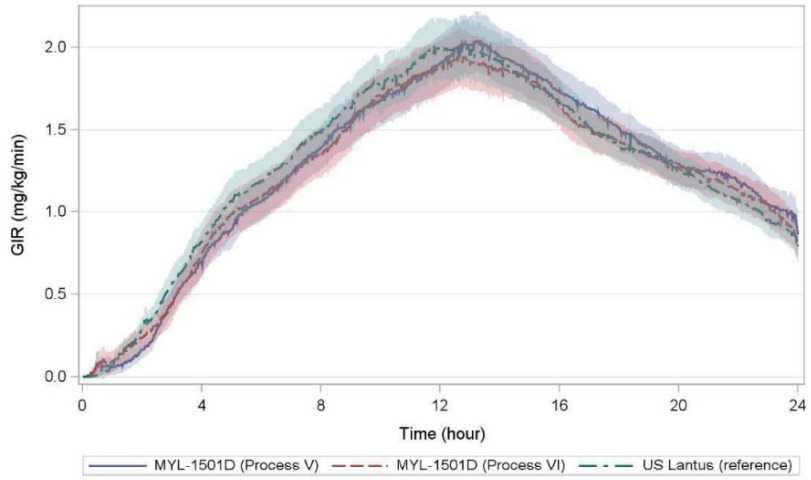


Figure 3. Mean GIR versus time profile by treatment in Study MYL-1501D-1003



PK/PD Similarity Study

Euglycemic clamp study in healthy subjects

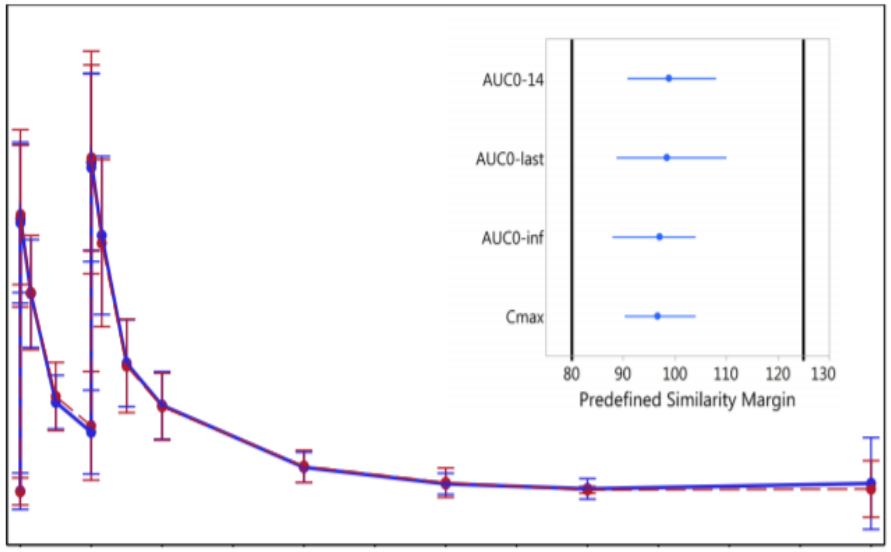
	Parameter	GMR (%)	90% CI
PK similarity	AUC0-24h	99.08	95.11 – 103.22
	Cmax	99.63	94.94 – 104.55
PD similarity	GIR AUC0-24h	94.92	86.95 – 103.62
	GIRmax	96.44	89.33 – 104.11

Adapted from the Multi-Discipline Review available on drugs@FDA

Clinical Program Example 2: CT-P10 vs US-Rituximab

PK Similarity Study in patients with rheumatoid arthritis using the therapeutic dosing

Mean (SD) serum concentration (mcg/mL)



Time (Days)

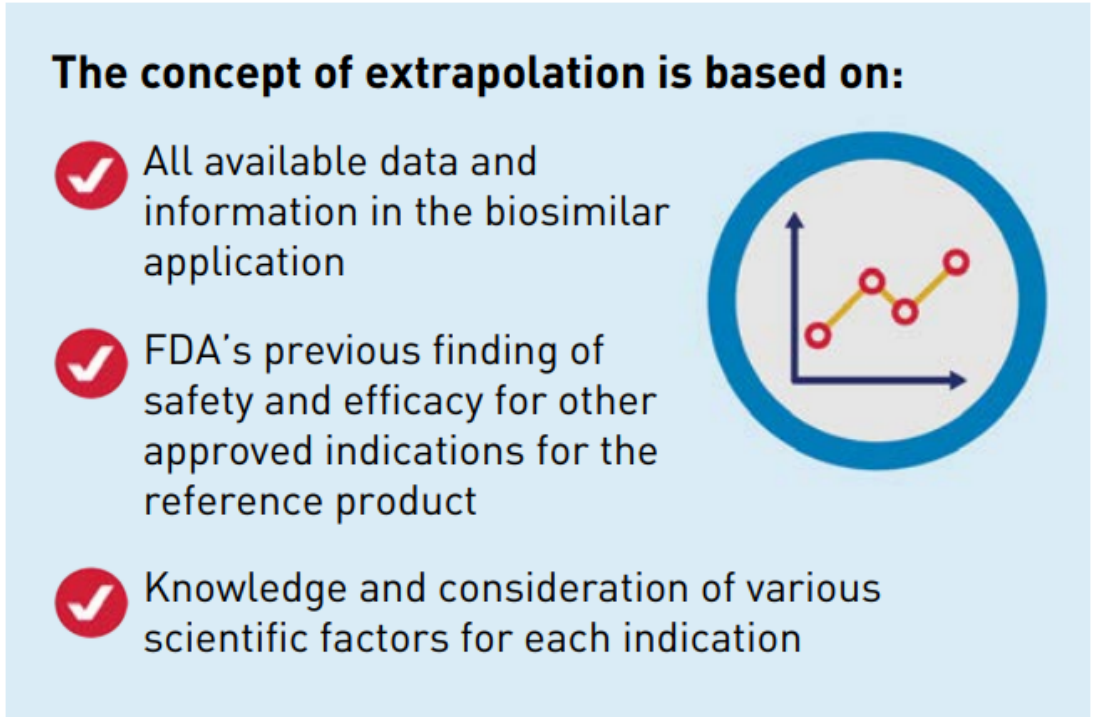
Comparative Clinical Study in patients with low tumor burden follicular lymphoma for comparing efficacy, safety, and immunogenicity

	CT-P10	US-Rituxan
Overall Response, n (%)	108/130 (83.1%)	104/128 (81.3%)
ORR Difference, (90% CI)	0.7981-1.0796	
Equivalence margin	0.83 – 1.17	
Immunogenicity	Similar	
Adverse events	Similar	

Adapted from Oct. 10, 18 FDA ODAC Slides: Slides from the October 10, 2018 Meeting of the Oncologic Drugs Advisory Committee

Rituximab-abbs (CT-P10) Licensed for Multiple Indications [1, 2]:

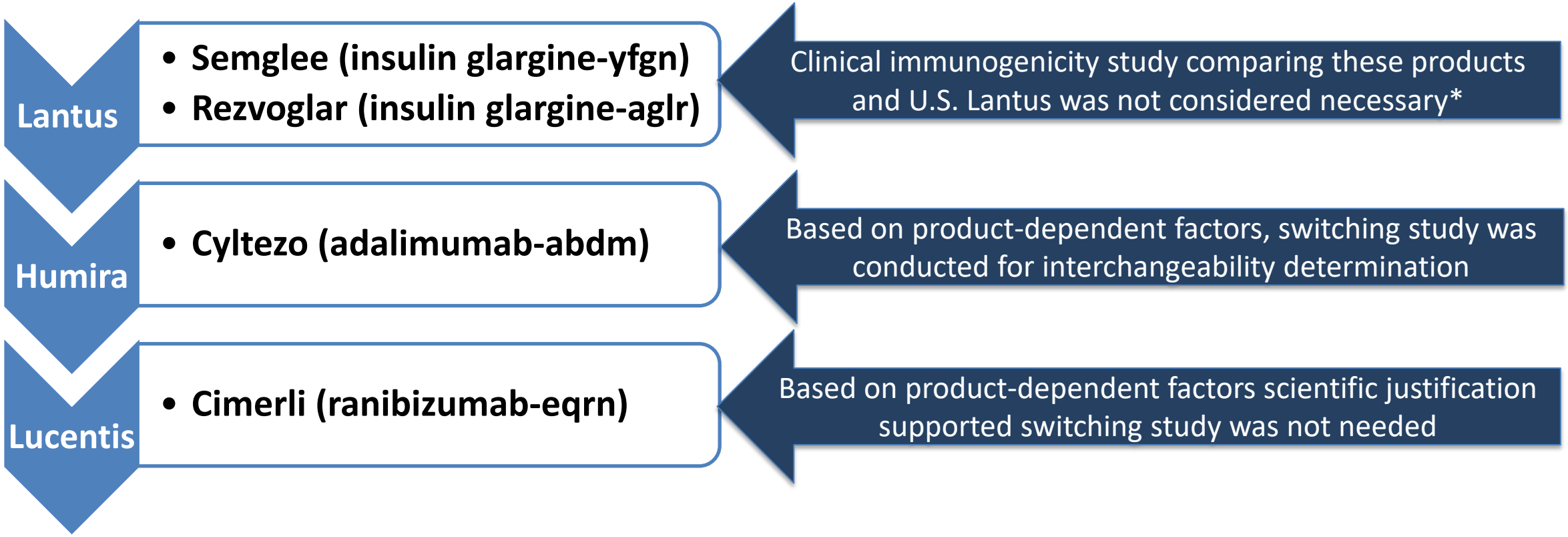
- Adult patients with Non-Hodgkin's Lymphoma (NHL)
- Adult patients with Chronic Lymphocytic Leukemia (CLL)
- Rheumatoid Arthritis (RA)
- Granulomatosis with Polyangitis (GPA) and Microscopic Polyangiitis (MPA) in adult patients



[1] See USPI for full indication text: Nov 28, 2018 USPI
[2] See USPI for full indication text: Feb 04, 2022 USPI

Interchangeable Biosimilars

To date, FDA has approved 4 interchangeable biosimilars to 3 different reference products



*Draft Guidance for Industry: Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products, 2019 https://www.fda.gov/media/133014/download; Review Documents available at: Drugs@FDA: FDA-Approved Drugs

Switching Between Products – Literature Highlights & Conclusions

- Reviews* of randomized and real-world studies do not suggest that switching from a reference product to a biosimilar results in efficacy, safety, or immunological issues
- Reviews# of randomized and real-world studies show that single or multiple switches between the reference product and its biosimilars had no negative impact on efficacy, safety, or immunogenicity
- Nocebo effect: Some studies report higher discontinuations in switched patients based on patient-reported outcomes without changes in objective parameters

- **Based on available data from randomized and real-world studies, no differences are observed in efficacy, safety, or immunogenicity following one or more switches, with the exception of nocebo effects.**
- **Theoretical safety and immunological concerns with switching have not been demonstrated in patients**

*Selected publication: Barbier et al. 2020 reviewed 178 studies with one or more switches between RP and BP totaling nearly 21,000 switched patients.
#Selected publication: Kurki et al. 2021 includes analyses for 23 biosimilar mAb and fusion proteins and represents over 2 billion treatment days

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 and interchangeable product* and prescribe them by name, just as for the reference product.

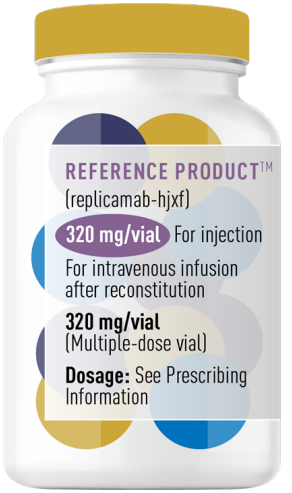
- Biosimilar and interchangeable biosimilar products can be used in patients who have previously been treated with the reference product (i.e., treatment-experienced), and in patients who have not previously been treated with the reference product (i.e., treatment-naïve).

- Interchangeable biosimilars may be substituted for the reference product without the intervention of the prescribing health care provider, subject to state laws.

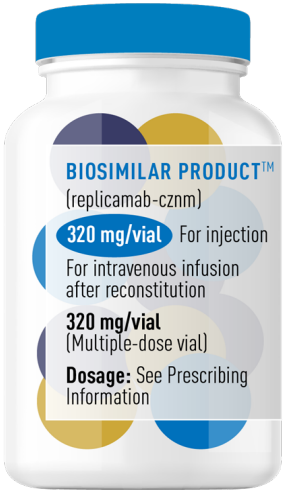
Biosimilar and Interchangeable Labeling

- The labeling summarizes the scientific information health care practitioners need for safe and effective use of the product.
- A biosimilar is not required to have the same labeling as its reference product (e.g., a biosimilar can be labeled for fewer than all conditions of use or there may be differences in storage/preparation, or presentation).
- Health care professionals are advised to review the labeling (i.e., prescribing information) of the biosimilar to determine the conditions of use (e.g., indications, dosing regimens) and routes of administration for which the biosimilar is approved.
- FDA recommends that Highlights of Prescribing Information contain a "Biosimilarity Statement" describing the product's relationship to its reference product.

Reference Product



Biosimilar Product



Biosimilar Labeling cont.

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use PROPRIETARY NAME safely and effectively. See full prescribing information for PROPRIETARY NAME.

PROPRIETARY NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol
Initial U.S. Approval: YYYY
NEXSYMEO (replicamab-cznm) is biosimilar* to JUNEXANT (replicamab-hjxf).

WARNING: TITLE OF WARNING
See full prescribing information for complete boxed warning.

- **Text (4)**
- **Text (5.x)**

----------RECENT MAJOR CHANGES----------
Section Title, Subsection Title (x.x) M/YYYY
Section Title, Subsection Title (x.x) M/YYYY

----------INDICATIONS AND USAGE----------
PROPRIETARY NAME is a (insert FDA established pharmacologic class text phrase) indicated for … (1)

- Indication #1
- Indication #2
- Indication #3

----------DOSAGE AND ADMINISTRATION----------
- Text (2.x)
- Text (2.x)

----------DOSAGE FORMS AND STRENGTHS----------
- Strength 1, in a single-dose prefilled syringe
- Strength 1, in a single-dose prefilled autoinjector

----------CONTRAINDICATIONS----------
- Text (4)
- Text (4)

----------WARNINGS AND PRECAUTIONS----------
- Text (5.x)
- Text (5.x)

----------ADVERSE REACTIONS----------
Most common adverse reactions (incidence > x%) are text (6.x)

To report SUSPECTED ADVERSE REACTIONS, contact name of manufacturer at toll-free phone # or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Text (7.x)
- Text (7.x)

----------USE IN SPECIFIC POPULATIONS----------
*Biosimilar means that the biological product is approved based on data demonstrating that it is highly similar to an FDA-approved biological product, known as a reference product, and that there are no clinically meaningful differences between the biosimilar product and the reference product. Biosimilarity of NEXSYMEO as been demonstrated for the condition(s) of use (e.g., indication(s), dosing regimen(s)), strength(s), dosage form(s), and route(s) of administration described in its Full Prescribing Information.

Revised: M/YYYY

Key Takeaways

Fact: FDA-approved biosimilars are as safe and effective as their original biologic and you can expect biosimilars to have the same benefits and risks as the original biologic.

Fact: FDA's approval of an interchangeable biosimilar does not indicate a higher standard than biosimilarity (all interchangeables are also biosimilar), but that it underwent further evaluation to allow it to be substituted for the reference product without consulting the health care prescriber.

Fact: Patients and healthcare providers do not need to wait for a biosimilar product to be approved as an interchangeable product. Biosimilars are safe and effective, just like the reference product to which they were compared.

Fact: Biosimilar and Interchangeable labeling is not required to be the same as the reference product, but is expected to incorporate relevant data and information from reference product labeling.

Resources for Health Care Providers

Purple Book:

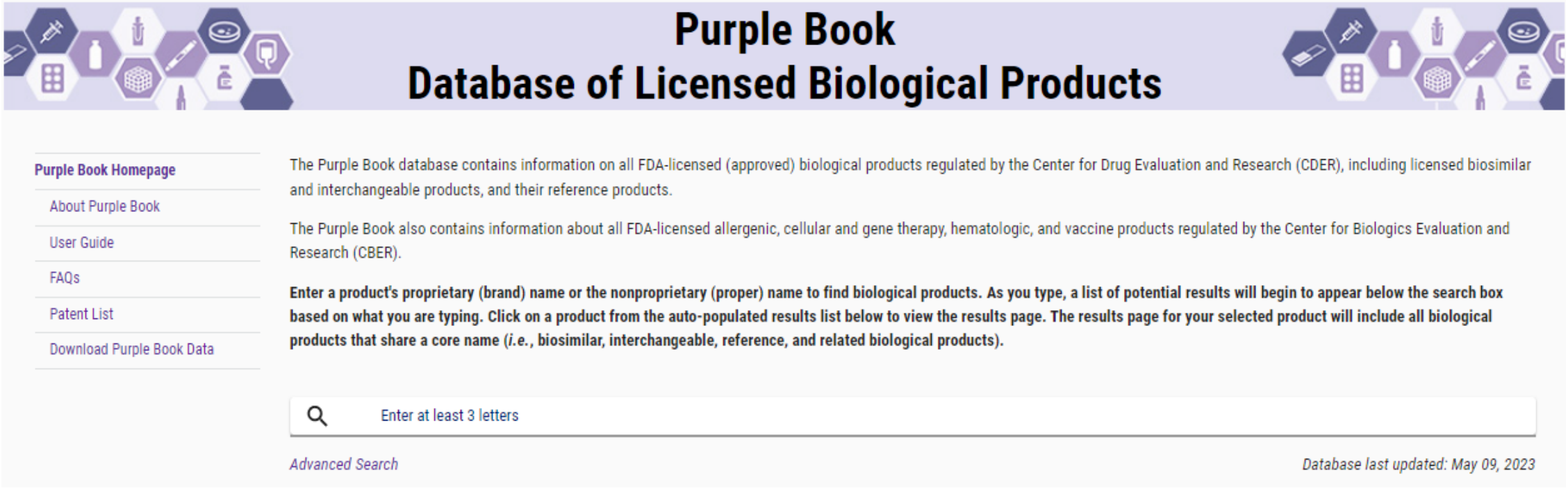
Database of Licensed Biological Products

The Purple Book Database

The Purple Book Database contains information on all FDA-licensed (approved) biological products regulated by the Center for Drug Evaluation and Research (CDER), including licensed biosimilar and interchangeable products, and their reference products.

The Purple Book also contains information about all FDA-licensed allergenic, cellular and gene therapy, hematologic, and vaccine products regulated by the Center for Biologics Evaluation and Research (CBER).

The database can be found at PurpleBookSearch.fda.gov



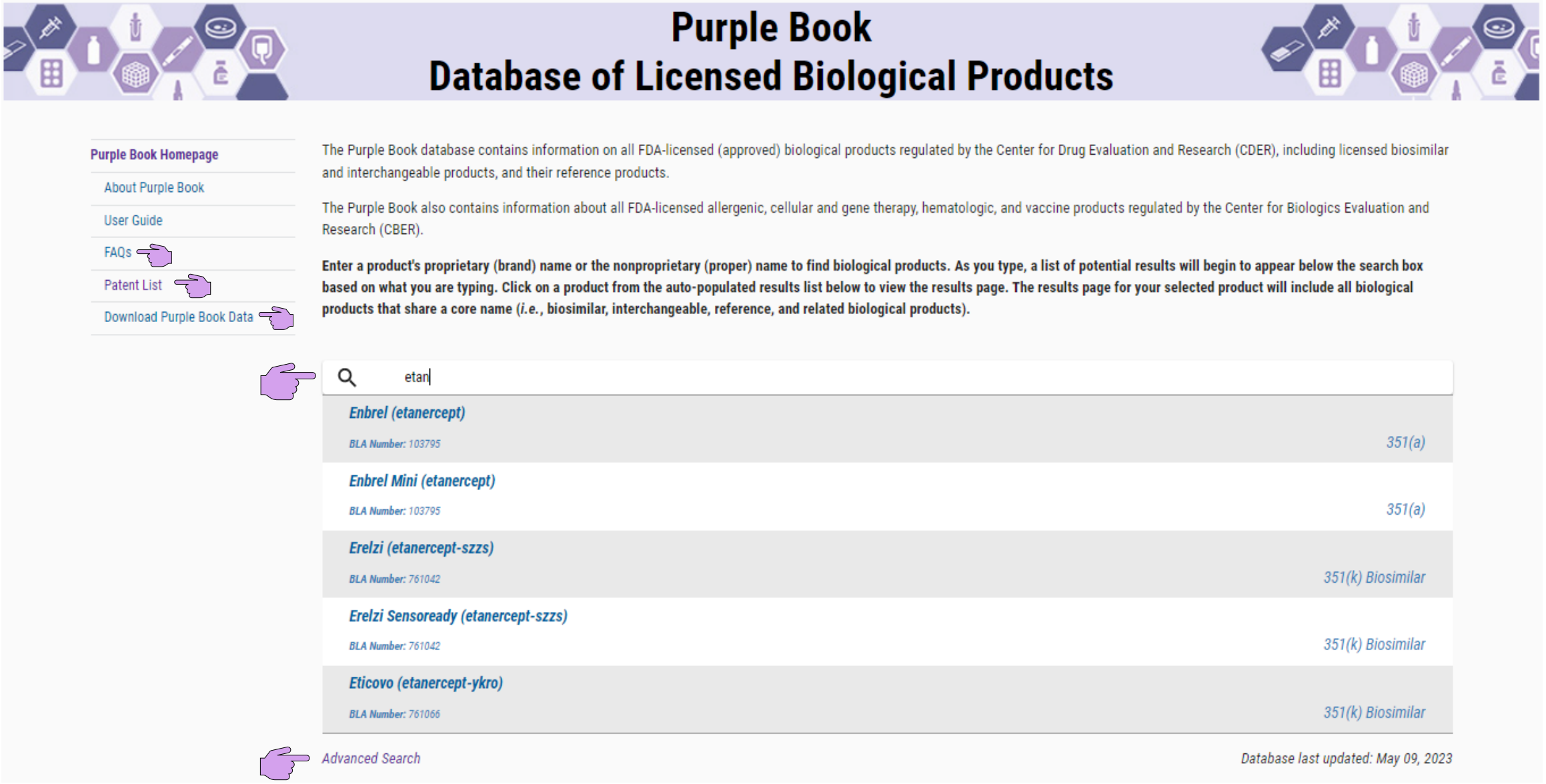
Purple Book's Features

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, and their reference products.

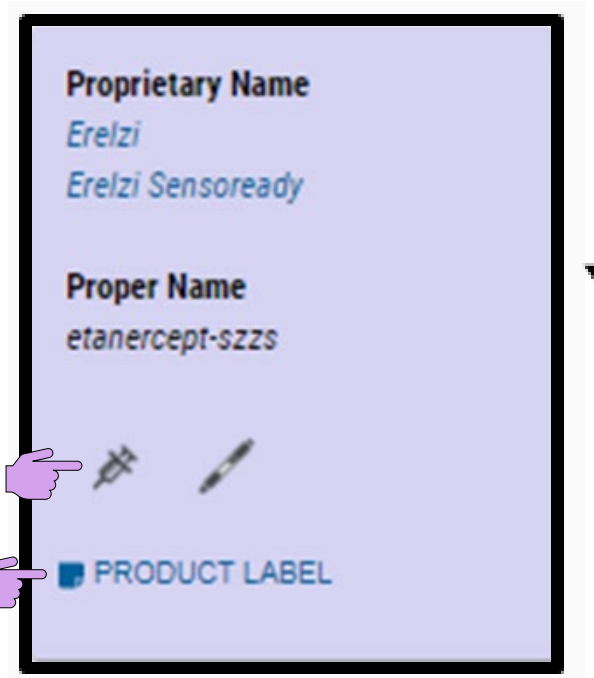
Features tailored to different user needs, including:

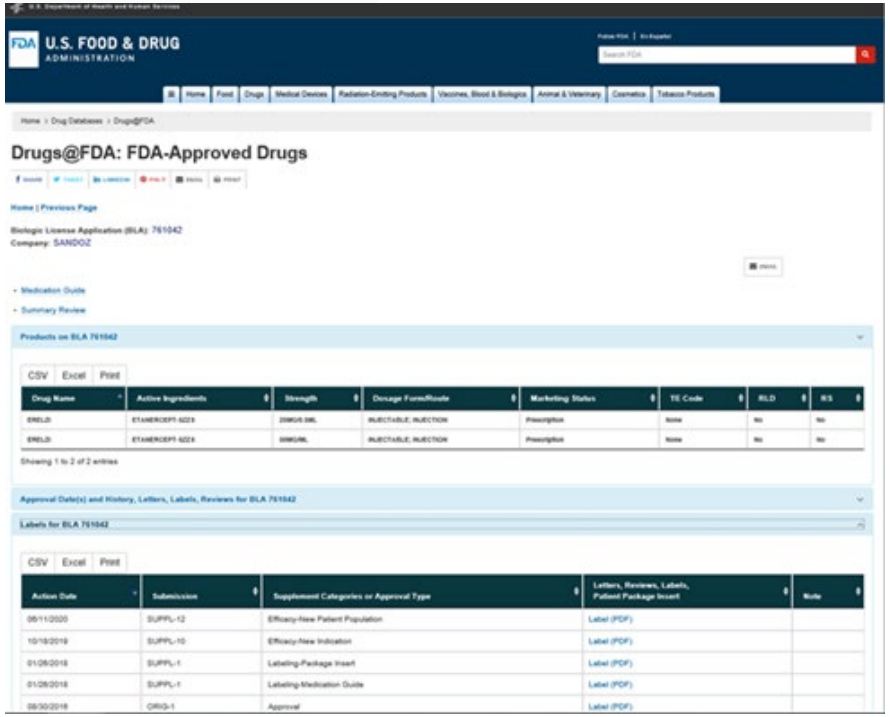
- Simple Search and Advanced Search
- User Guide with detailed instructions for site location functions
- Auto-populated search results
- Additional advanced search filters
- Data download and export options
- Product label links
- Show/hide sortable data column options
- Searchable glossary of terms

Homepage & Simple Search



Simple Search Results





Purple Book
Database of Licensed Biological Products

Simple Search Results for: *Erelzi* NEW SEARCH | Navigate to Advanced Search

The Simple Search Results page for the selected product includes all biological products that share a core name (*i.e.*, biosimilar, interchangeable, reference, and related biological products).

Matching card colors indicate a biological product is biosimilar to or interchangeable with a reference product.

Biosimilar(s)

Proprietary Name
Erelzi
Erelzi Sensoready
Proper Name
etanercept-szzs
PRODUCT LABEL

Proprietary Name
Eticovo
Proper Name
etanercept-ykro
PRODUCT LABEL

Interchangeable(s)

No interchangeable data at this time.

Reference Product(s)

Proprietary Name
Enbrel
Enbrel Mini
Proper Name
etanercept
PRODUCT LABEL

To view a list and definitions of Product Presentation icons (e.g., ,), click here. Hover over icons to view additional information.

Grayed out Product Label links indicate that there is no product label available for the product.

Product Details

Purple Book
Database of Licensed Biological Products

- Purple Book Homepage
- About Purple Book
- User Guide
- FAQs
- Patent List
- Download Purple Book Data

Product Details for: *Erelzi, Erelzi Sensoready*

< RETURN TO SEARCH RESULTS

Product Label

Grayed out Product Label links indicate that there is no product label available for the product.

Product Number	Dosage Form	Route of Administration	Strength	Product Presentation	License Type	Proprietary Name	Status
001	Injection	Subcutaneous	25MG/0.5ML	Pre-Filled Syringe	351(k) Biosimilar	Erelzi	Rx
002	Injection	Subcutaneous	50MG/ML	Pre-Filled Syringe	351(k) Biosimilar	Erelzi	Rx
003	Injection	Subcutaneous	50MG/ML	Autoinjector	351(k) Biosimilar	Erelzi Sensoready	Rx

Proper Name
etanercept-szzs

Reference Product Proper Name
etanercept

Reference Product Proprietary Name
Enbrel

BLA Number
761042

Applicant
Sandoz Inc.

Original Approval Date
08/30/2016

Date of First Licensure

< RETURN TO SEARCH RESULTS

Advanced Search

Purple Book
Database of Licensed Biological Products

- Purple Book Homepage
- About Purple Book
- User Guide
- FAQs
- Patent List
- Download Purple Book Data

Advanced Search

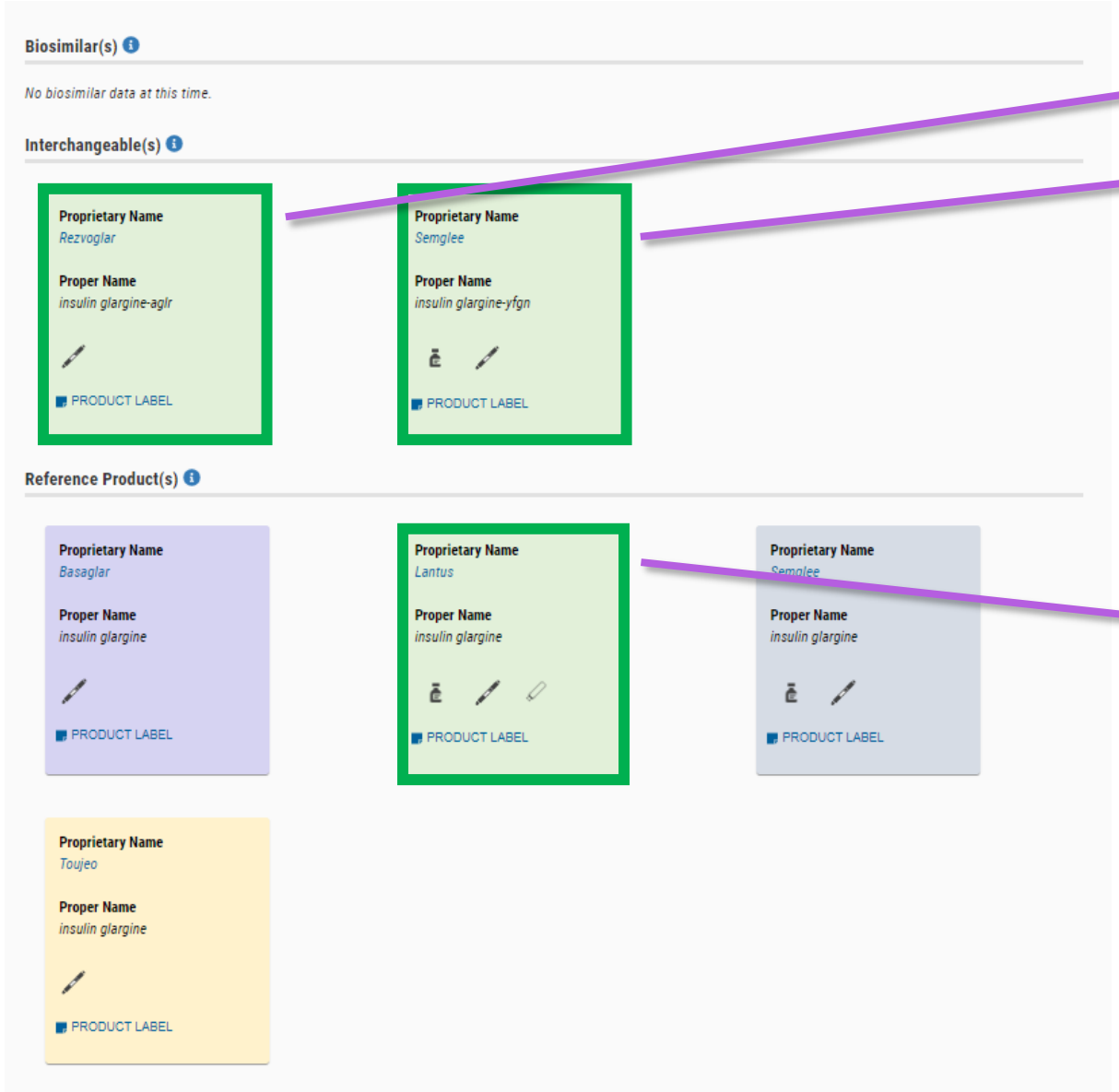
Enter data into the search box to search all products in the Purple Book. Click 'Additional Search Filters' to expand your search by entering additional terms or selecting from the drop-down list. The Advanced Search table below will update in real time and display all products that match any of the terms entered.

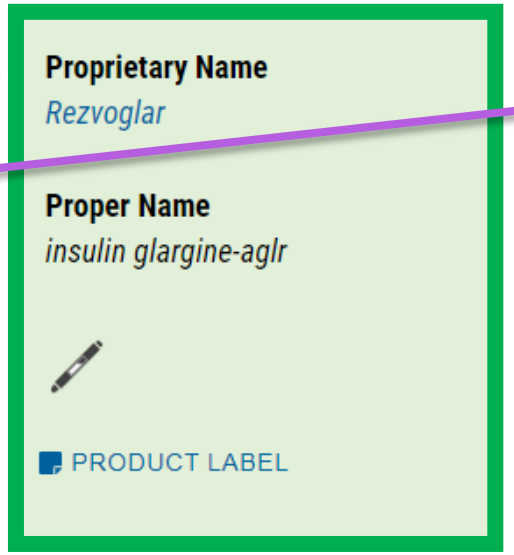
Search etaner RESET

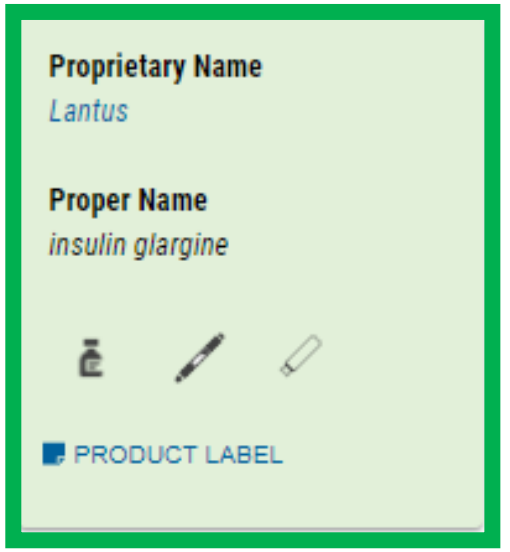
Showing 1 to 12 of 12 rows 50 rows per page

Product Label	Applicant	Proprietary Name	Proper Name	License Type	Strength	Dosage Form	Route of Administration	Product Presentation	Status
	Immunex Corporation	Enbrel	etanercept	351(a)	25MG	For Injection	Subcutaneous	Single-Dose Vial	Disc
	Immunex Corporation	Enbrel	etanercept	351(a)	25MG	For Injection	Subcutaneous	Multi-Dose Vial	Rx
	Immunex Corporation	Enbrel	etanercept	351(a)	50MG/ML	Injection	Subcutaneous	Pre-Filled Syringe	Rx
	Immunex Corporation	Enbrel	etanercept	351(a)	25MG/0.5ML	Injection	Subcutaneous	Pre-Filled Syringe	Rx
	Immunex Corporation	Enbrel	etanercept	351(a)	25MG/0.5ML	Injection	Subcutaneous	Single-Dose Vial	Rx
	Immunex Corporation	Enbrel	etanercept	351(a)	50MG/ML	Injection	Subcutaneous	Autoinjector	Rx
	Immunex Corporation	Enbrel Mini	etanercept	351(a)	50MG/ML	Injection	Subcutaneous	Single-Dose Cartridge	Rx
	Sandoz Inc.	Erelzi	etanercept-szzs	351(k) Biosimilar	25MG/0.5ML	Injection	Subcutaneous	Pre-Filled Syringe	Rx
	Sandoz Inc.	Erelzi	etanercept-szzs	351(k) Biosimilar	50MG/ML	Injection	Subcutaneous	Pre-Filled Syringe	Rx

Interchangeable Products

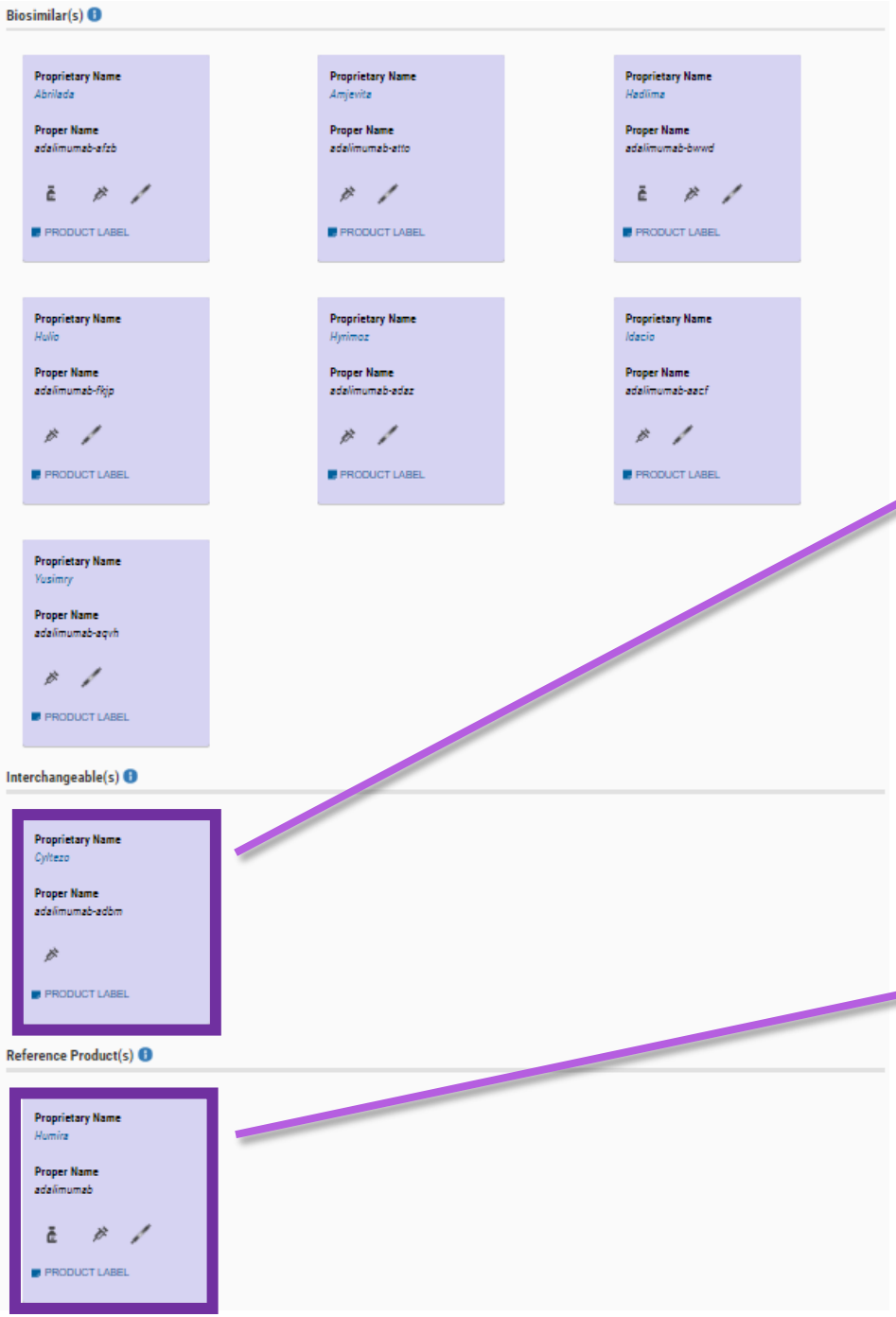


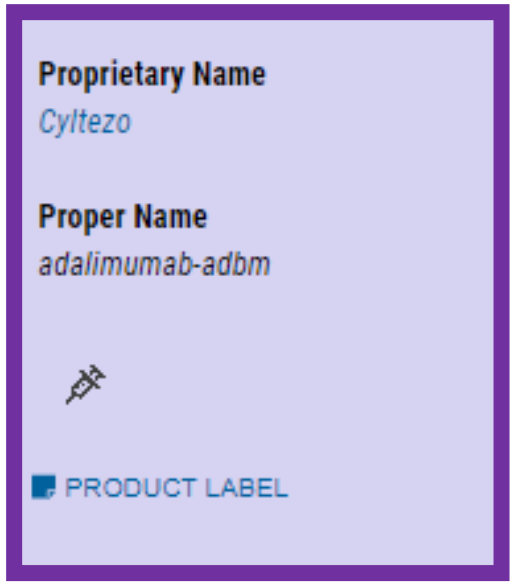




https://purplebooksearch.fda.gov

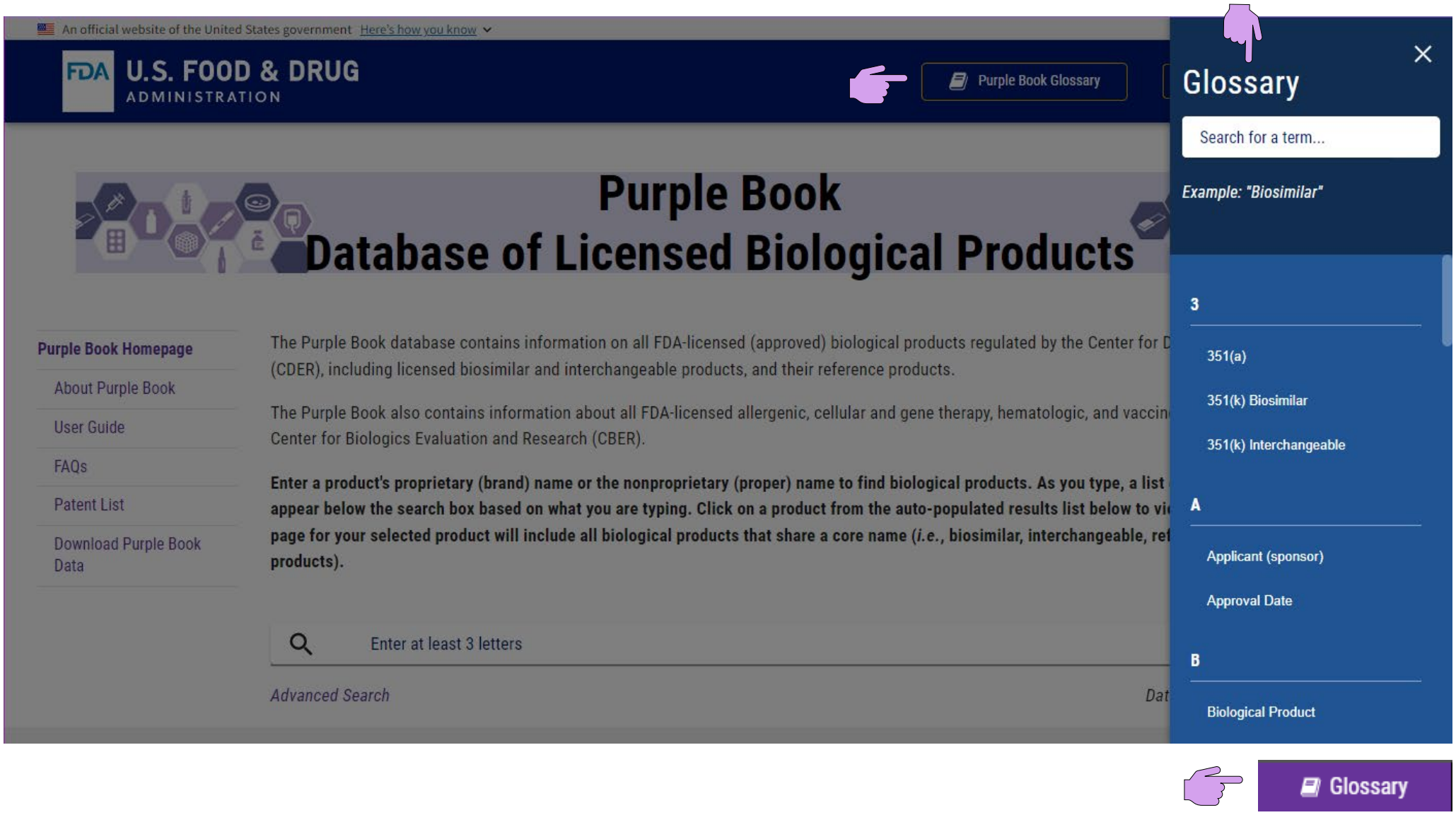
Interchangeable Products, Continued





https://purplebooksearch.fda.gov

Glossary of Terms



Biosimilar Education and Outreach

Education and Outreach

- FDA is committed to developing effective communications 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 is committed to fulfilling their important role as one of many stakeholders

Communication Challenges

- Lack of awareness and information gaps
- Low health literacy
- Concerns about safety and efficacy
- Lack of trust
- Concerns about cost and equivalency to existing treatment
- Negative perceptions and expectations leading to nocebo effect

Health Care Provider Materials

U.S. FOOD & DRUG ADMINISTRATION

Biosimilar Regulatory Review and Approval

Biological products (biologics) are the fastest-growing class of medications in the United States and account for a substantial and growing portion of health care costs. The Biologics Price Competition and Innovation Act of 2009 created an abbreviated approval pathway to provide patients with greater access to safe and effective biological products. This pathway helps reduce the time and cost of development without compromising safety and effectiveness.

Overview of the Approval Process

- All FDA-approved biologics undergo a rigorous evaluation so that health care providers and patients can be confident of the safety, effectiveness, and quality of these products.
- A biosimilar is a biologic that is highly similar to and has no clinically meaningful differences from an existing FDA-approved biological medication, called a reference product.
- A reference product is approved in a standalone application that must contain all data and information necessary to demonstrate the product's safety and effectiveness.
- The goal of a biosimilar development program is to demonstrate biosimilarity between the proposed biosimilar and its reference product, not to independently establish the safety and effectiveness of the proposed biosimilar. This generally means that biosimilar manufacturers do not need to conduct as many expensive and lengthy clinical trials.
- The abbreviated pathway involves an extensive structural and functional comparison of the biosimilar and the reference product.
- Because biologics are usually made in cells, even with identical amino acid sequences, there will be inherent variations (for example, glycosylation) that result from the manufacturing process in any batch or dose.
- As part of the approval process for both reference products and biosimilars, FDA assesses a manufacturer's strategy to control for the pattern and degree of variations between different batches so that safety and effectiveness don't change.
- FDA monitors the safety and effectiveness of all medications after their approval. This involves inspecting manufacturing facilities and reviewing manufacturer, provider, and patient safety reports made to FDA.

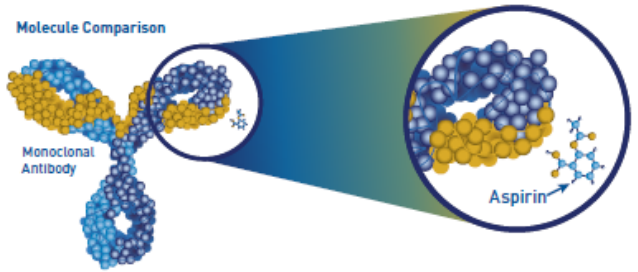
U.S. FOOD & DRUG ADMINISTRATION

Overview of Biosimilar Products

Biosimilars are safe and effective biological medications for treating many illnesses, including chronic skin diseases, such as psoriasis; inflammatory bowel diseases, such as Crohn's disease and ulcerative colitis; arthritis; kidney conditions; diabetes; and cancer. These medications can provide more treatment options and potentially reduce costs for patients.

Biosimilars Are Biological Products

- Biological products, or biologics, are generally large, complex molecules that are made from living sources such as bacteria, yeast, and animal cells. On the other hand, drugs made from chemicals are smaller molecules and easier to copy.
- Because they generally come from living organisms, biologics inherently contain many slight variations from batch to batch, and their structures are generally more complex than those of other medications. As a result, biologics are often more complicated to purify, process, and manufacture.
- There are many types of biologics approved for use in the United States, including therapeutic proteins; vaccines; blood, blood components, and their derivatives; allergenic products; and monoclonal antibodies.



U.S. FOOD & DRUG ADMINISTRATION

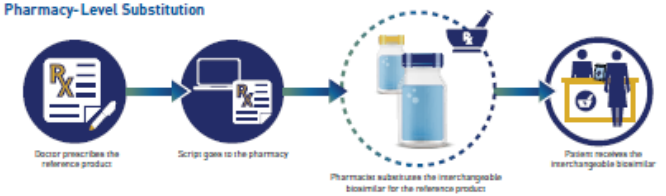
Interchangeable Biological Products

An interchangeable biological product is a biosimilar that meets additional requirements and may be substituted for the reference product at the pharmacy, depending on state pharmacy laws. Interchangeable biological products (also called interchangeable biosimilars or interchangeable products) may help increase patient access to biologics.

Interchangeable Biosimilars

- An interchangeable biosimilar may be substituted at the pharmacy for the reference product without the intervention of the prescribing health care provider — much like how generic drugs are routinely substituted for brand-name drugs.
- Not all biosimilars are interchangeable. Companies must submit an application with adequate information to support an interchangeability determination for their product to be approved as an interchangeable biosimilar.

Pharmacy-Level Substitution



Interchangeable Biosimilar Approval Process

- Unlike a reference product, which is approved in a standalone application, all biosimilar and interchangeable biosimilars are approved through an abbreviated pathway that compares the product to the reference product to show biosimilarity.
- For approval as an interchangeable biosimilar, manufacturers must provide additional data that reflect how the interchangeable biosimilar may be used in the marketplace with patients. Like generic drugs, patients receiving their medications through their pharmacies may switch between a brand-name biologic and an interchangeable biosimilar.
- To assess the safety of switching, manufacturers generally conduct studies in which patients alternate between the reference product and the interchangeable biosimilar and compare those patients to patients who are just being treated with the reference product. The results must show no decrease in effectiveness or increase in safety risk associated with switching.
- While this additional information helps FDA to determine the safety of pharmacy-level substitution, this does not mean that an interchangeable biosimilar is safer or more effective than other biosimilars.

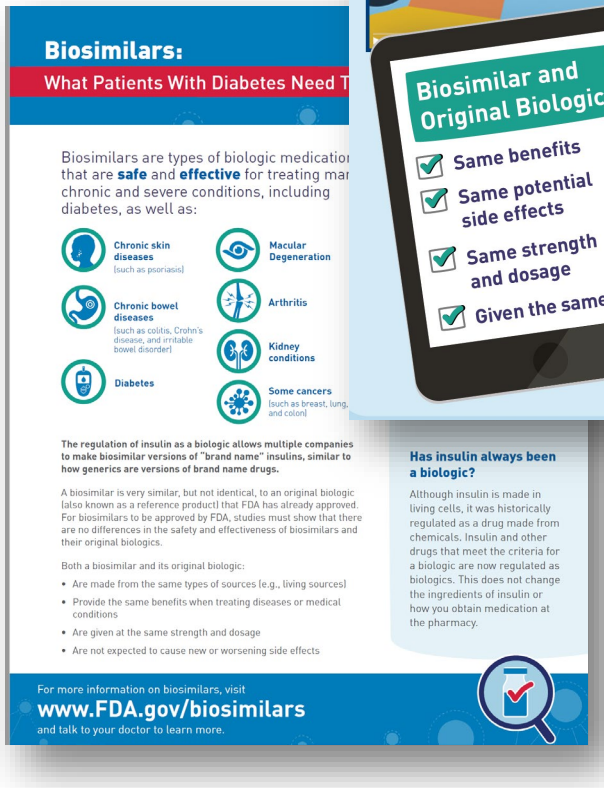
All biological products are approved only after they meet FDA's rigorous approval standards, so health care professionals and patients can be confident in the safety and effectiveness of a biosimilar product, whether or not it has also been approved as an interchangeable biosimilar, just as they would be for a reference product.

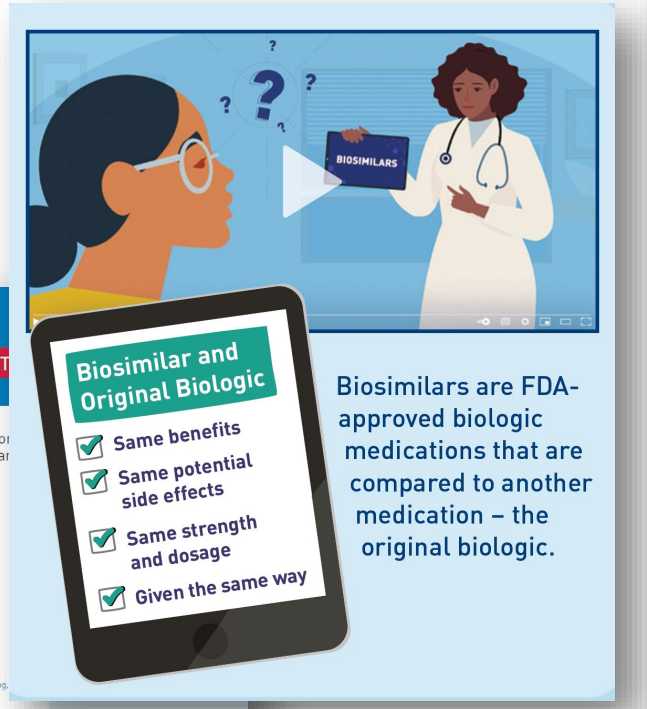
Explore FDA's biosimilar resources for health care professionals at www.fda.gov/biosimilars.

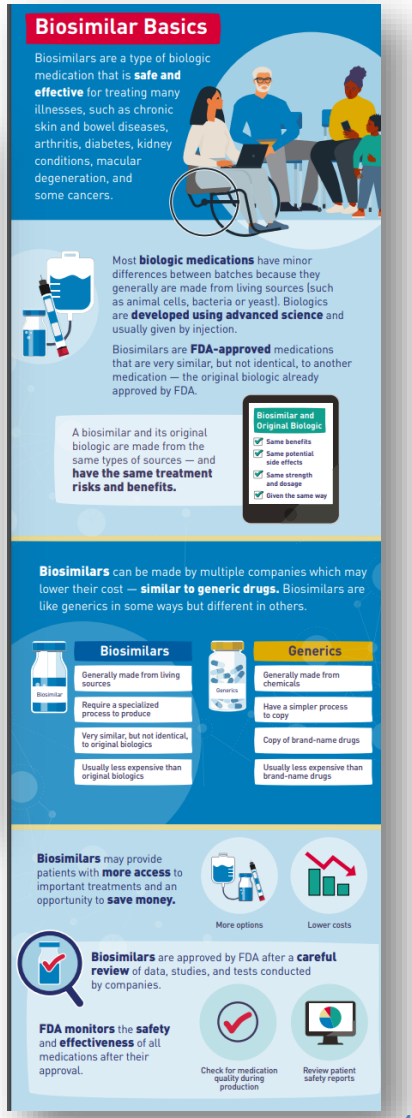
FDA Biosimilar Materials for Patients

www.fda.gov/drugs/biosimilars/basics-patients

- English and Spanish fact sheets, infographics, articles, and more







FDA Biosimilar Materials in Spanish

Artículos en español

- Alimentos y Bebidas
- Cosméticos
- Dispositivos Médicos
- Dispositivos que Emiten Radiación
- Fraude en la Salud
- Medicamentos
- Nutrición
- Productos de Tabaco
- Productos Veterinarios
- Salud de la Mujer
- Salud Infantil
- Vacunas, Sangre y Productos Biológicos

English

La Administración de Alimentos y Medicamentos de los EE.UU. (FDA, por sus siglas en inglés) ha aprobado medicamentos biosimilares para tratar enfermedades como el cáncer, la enfermedad de Crohn, la colitis, la artritis reumatoide, la psoriasis y otras.

Pero, ¿qué son los medicamentos biosimilares y biológicos intercambiables? Para

Curriculum for Health Care Degree Programs

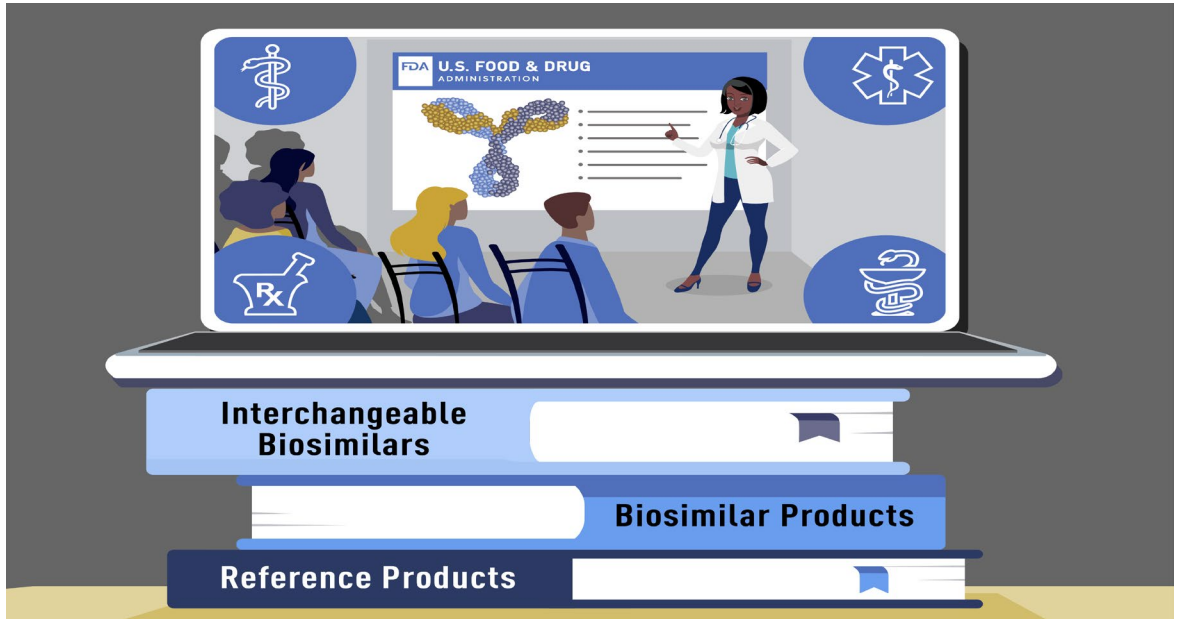
- The Biosimilar Curriculum Toolkit contains multiple types of resources to assist teaching faculty who would like to integrate topics about biosimilars into the training they provide students.

- The materials included in the toolkit were designed to meet a variety of teaching needs and contain foundational and more in-depth information by levels.

  — Level 1 is foundational and provides a high-level overview of foundational topics.

  — Level 2 materials provide an in-depth look at scientific and regulatory topics and their practical applications.

- Materials include information sheets, slide decks, videos, case studies, discussion questions, and more.

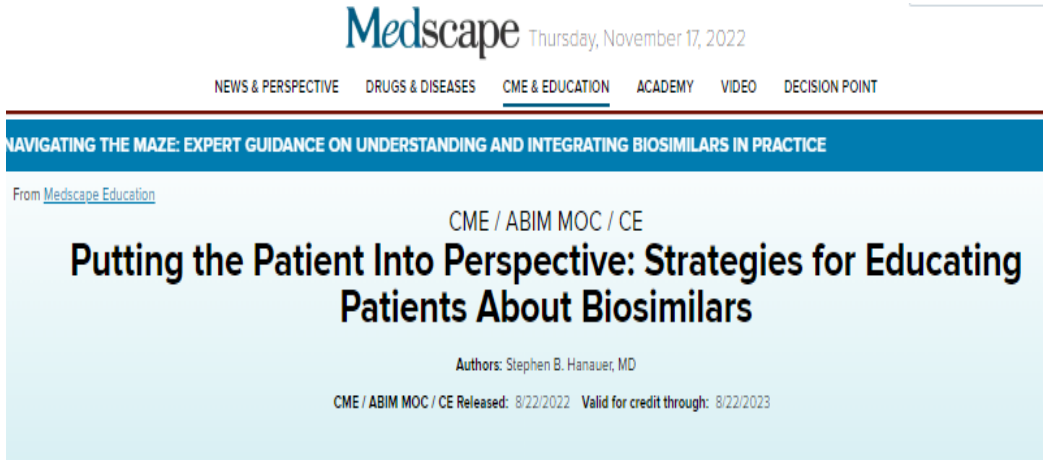


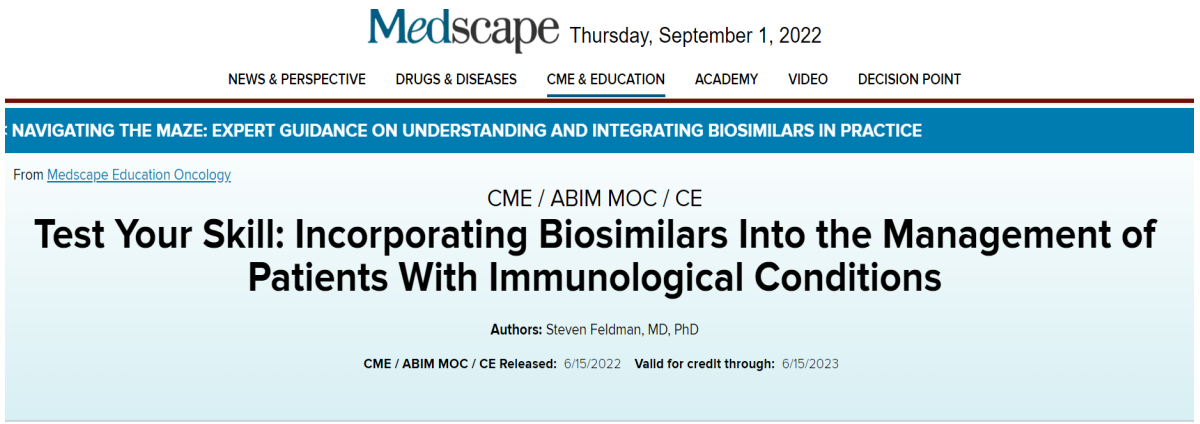
Topics covered:

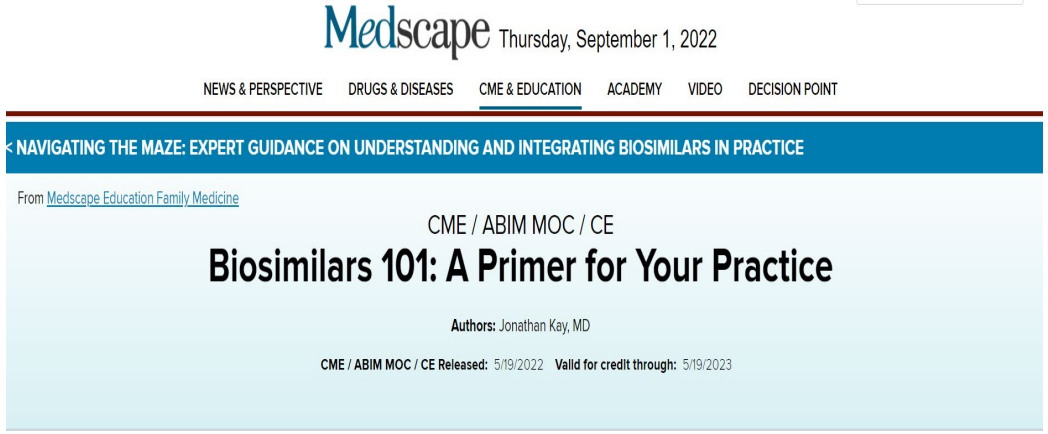
- Biologics, biosimilars, and interchangeability
- The approval pathways for biological products
- Manufacturing and variation in biological products
- Labeling and prescribing biosimilar and interchangeable biosimilar products

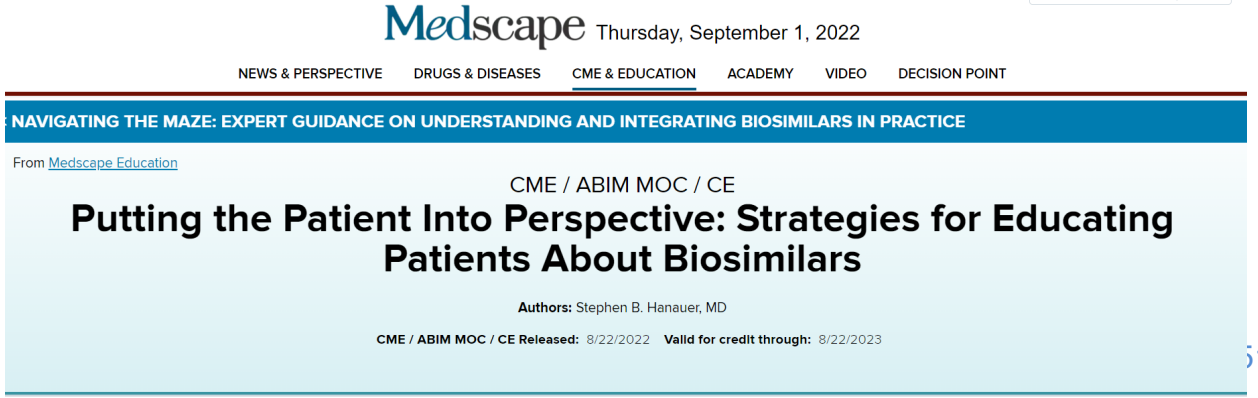
Medscape Continuing Education

FDA is supporting the development of a series of continuing education (CE) courses through Medscape about biosimilar and interchangeable products. This includes 4 courses in 2022 and a dedicated website for the content.







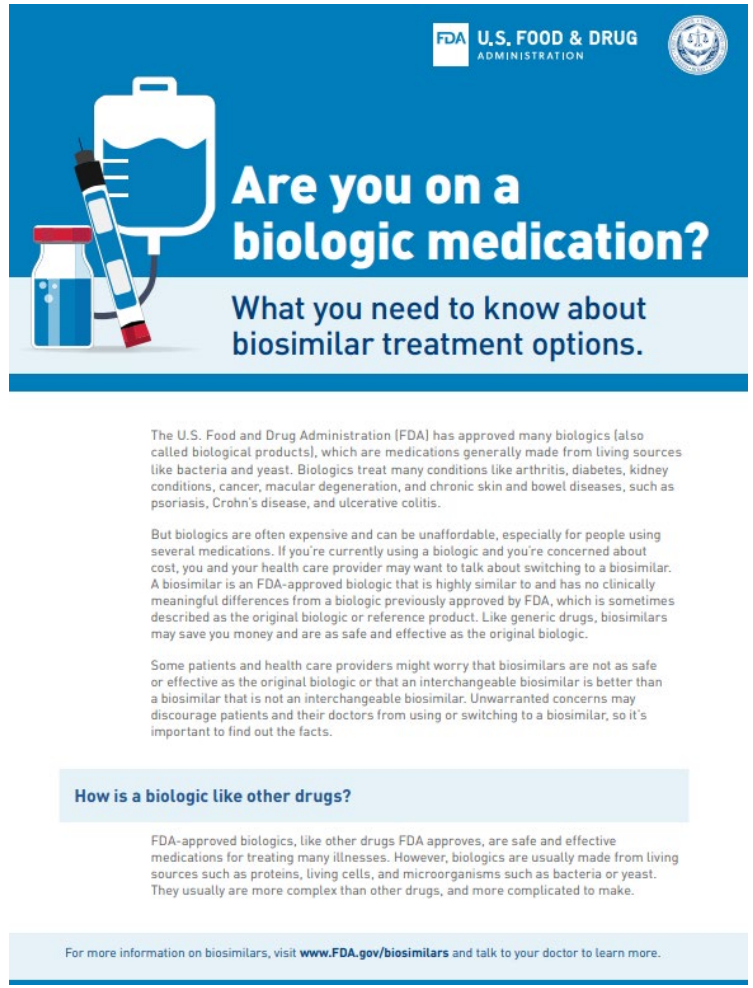


Stakeholder Engagement

FDA works with government and non-government stakeholders to support uptake and utilization of biosimilars.

- USP/FDA Infographic on biosimilars and quality
- FDA/ FTC educational resource for patients about biosimilar treatment options

Conducting stakeholder outreach and offering education to stakeholders including patient advocacy organizations, medical and professional associations, payors, pharmacy organizations, and state and federal governments partners.



Future Education and Outreach Plans

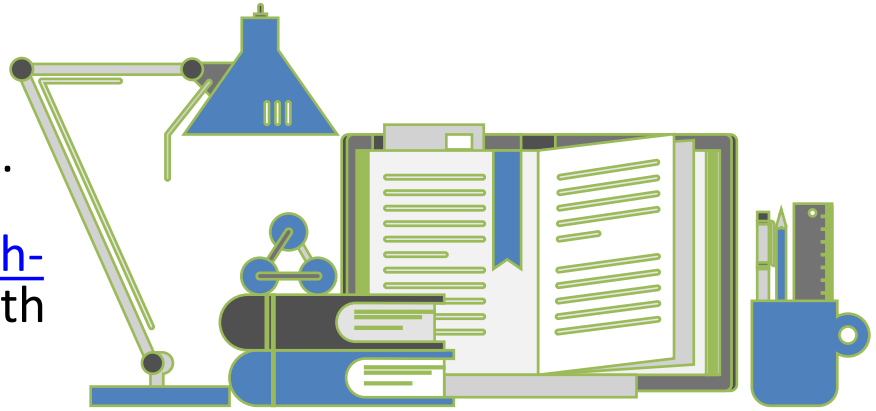
- Materials and resources for **patients**:
  - Videos
  - Additional infographics and graphics

- Materials and resources for **health care providers**:
  - Videos
  - More continuing Education course options through Medscape
  - Updated educational curriculum/teaching resources for HCP schools

- Continue work with multiple stakeholders to increase educational opportunities and ensure unbiased, truthful information about biosimilars is available.

Resources

- 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/drugs/biosimilars/curriculum-materials-health-care-degree-programs-biosimilars for curriculum materials for health care degree programs
- Guidance Webpage for guidance related to BsUFA, including details on BPCI (search on “biosimilar”)
- CDERLearn Training and Education for FDA CE, Medscape CE, and other education content- select "biosimilars" under topics.



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Questions?

Thank you

Visit **www.FDA.gov/biosimilars** to learn more about biosimilars.