FDA Drug Topics

Biosimilar and Interchangeable Biological Products: Basic Concepts and Practical Resources

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Overview

- Introduction to Biosimilar and Interchangeable Biological Products
  - Scientific and Regulatory Aspects
- FDA's Approach to the Development of Biosimilars
- Using Biosimilar and Interchangeable Products
- Progress To Date
  - Biosimilars Action Plan
- An Overview of The Purple Book: Database of Licensed Biological Products
- Resources for Health Care Providers

Learning Objectives

1. Describe how biologics differ from small molecules (size, complexity, manufacturing) and explain why some biologics cannot be copied exactly.
2. Compare and contrast the development, statutory requirements, and approval process for new biologics and for biosimilars/interchangeables.
3. Compare and contrast the requirements for generics and biosimilar/interchangeables and discuss the availability of insulin products.
4. Review a case study of an approved biosimilar product.
5. Describe and explain the new resources available for health care providers to learn more about biosimilar and interchangeable products through the enhanced Purple Book and other FDA educational resources.

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Introduction to Biosimilarity Concepts

Biosimilars Approved by FDA in 2020	
Nyvepria (pegfilgrastim-apgf)	**Hulio** (adalimumab-fkjp)
Riabni (rituximab-arrx)	
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 Approved by FDA in 2018	
*__Retacrit__ (epoetin alfa-epbx)	**Udenyca** (pegfilgrastim-cbqv)
Fulphila (pegfilgrastim-jmdb)	*__Truxima__ (rituximab-abbs)
Nivestym (filgrastim-aafi)	**Herzuma** (trastuzumab-pkrb)
Hyrimoz (adalimumab-adaz)	
Biosimilars Approved by FDA in 2017	
Renflexis (infliximab-abda)	*__Ogivri__ (trastuzumab-dkst)
Cyltezo (adalimumab-adbm)	**Ixifi** (infliximab-qbtx)
*__Mvasi__ (Bevacizumab-awwb)	
Biosimilars Approved by FDA in 2016	
*__Inflectra__ (infliximab-dyyb)	*__Amjevita__ (adalimumab-atto)
*__Erelzi__ (etanercept-szzs)	
Biosimilars Approved by FDA in 2015	
*__Zarxio__ (filgrastim-sndz)	

Biosimilars: Current Stats

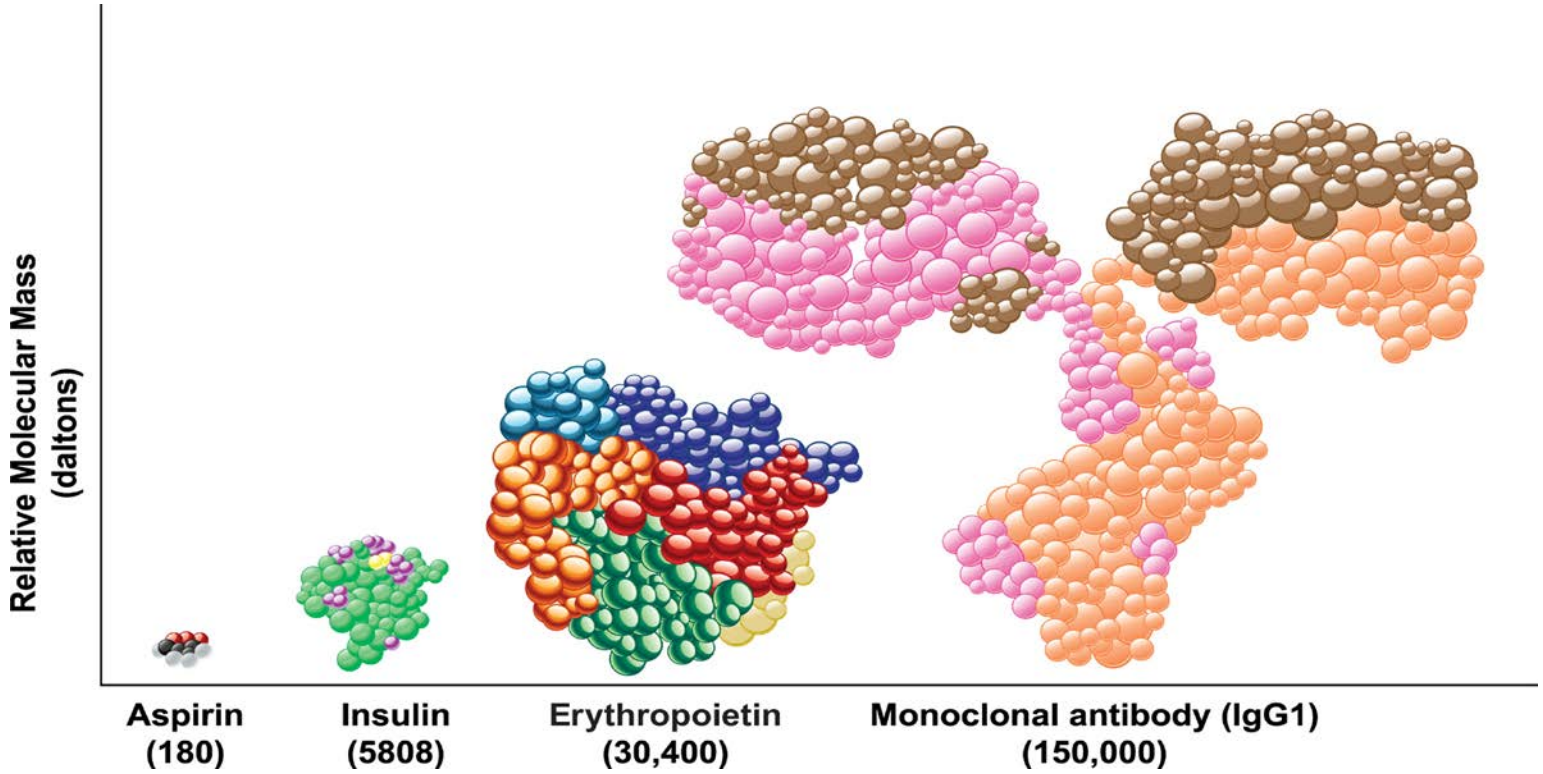
Reference Product	Approved = 29	Marketed = 19
Herceptin	5	5
Humira	6	0
Remicade	4	3
Neulasta	4	3
Neupogen	2	2
Avastin	2	2
Rituxan	3	3
Enbrel	2	0
Epogen	1	1

Highlighted = currently marketed

*Advisory Committee Meeting Held

Biological Products

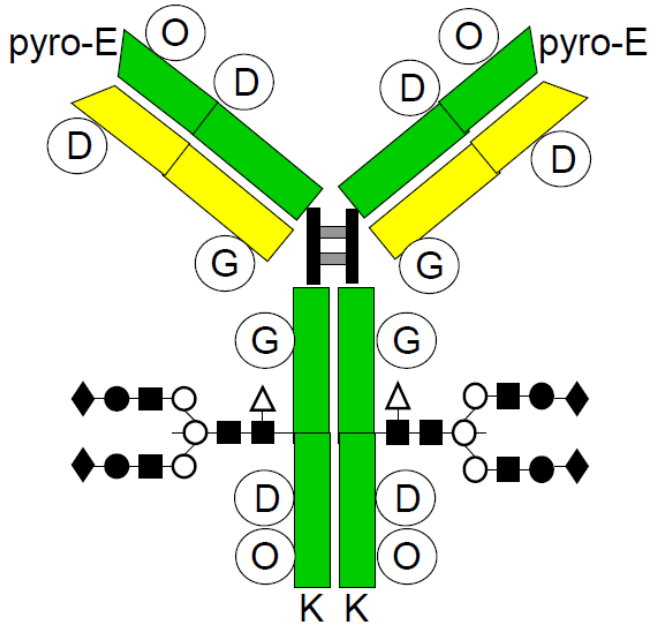
- Biologics are generally large and recombinantly produced from living systems
- They range in size and complexity
- Examples: therapeutic proteins, vaccines, monoclonal antibodies

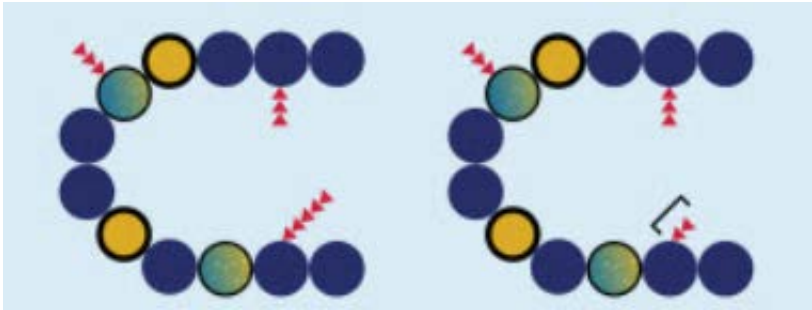


H Mellstedt. European Journal of Cancer Supplements. 2013;11:1-11.

Biological Products: Complexity

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





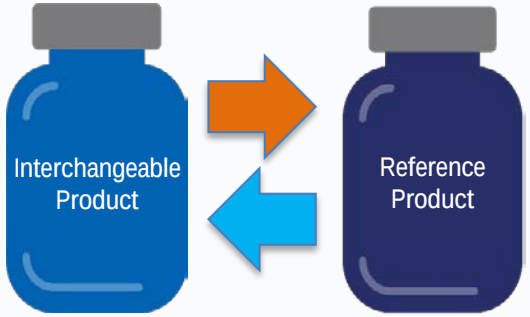
Basics of Biosimilarity

Reference Product (RP)

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

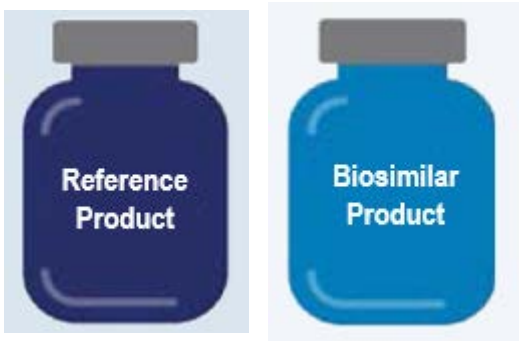


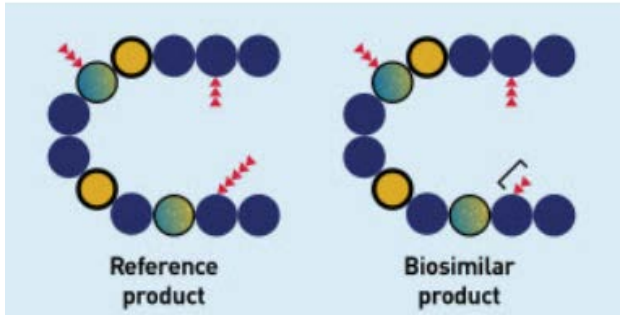
Interchangeable Product

An interchangeable is a biosimilar and expected to produce the same clinical result as the RP in any given patient. It can be substituted for the RP without the intervention of the prescribing health care provider

Can Most Biologics be Copied Exactly? No

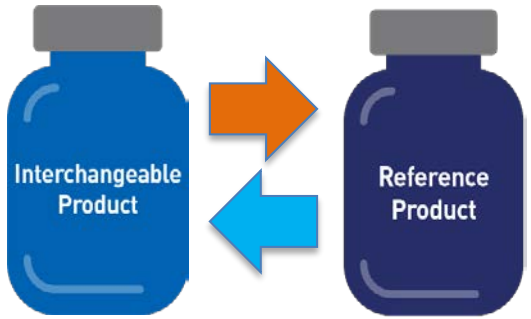
- Most biologics are mixtures of variants
- Using advanced scientific analysis, molecular patterns and profiles emerge
- Biosimilars try to match the patterns and variations of the reference product
- Both the reference product (RP) and biosimilar (BS) contain these variants and try to keep a consistent mix

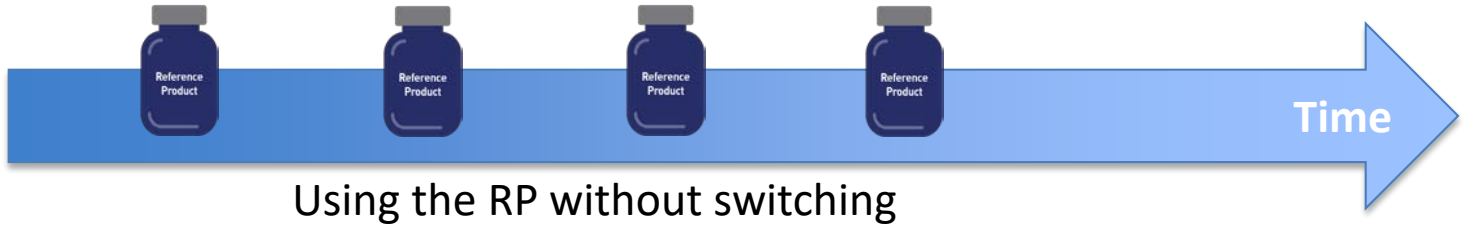




Standards for Interchangeable Biosimilar Products

- An interchangeable biosimilar product may be substituted for the RP without the intervention of the health care provider who prescribed the RP, subject to state laws
- Provide information or data intended to help inform what might happen with substitution:
  - Switching between the proposed product and the reference product does not increase safety risks or decrease effectiveness compared to using the reference product only
  - The proposed product can be expected to provide the same clinical result as the reference product in “any given patient”





Using the RP without switching

Switching between the proposed product and the RP

Transition Biological Products

- Some protein products historically were approved in new drug applications under section 505(c) of the FD&C Act
  - e.g., insulin and insulin analogs, somatropin, pancreatic enzyme products, and certain reproductive hormones

- BPCI Act amended the definition of "biological product" in section 351(i) of the PHS Act to include a "protein (except any chemically synthesized polypeptide)"

- The Further Consolidated Appropriations Act, 2020, further amended the definition of "biological product" in section 351(i) of the PHS Act to remove the parenthetical "(except any chemically synthesized polypeptide)" from the statutory category of "protein"

Transition Biological Products cont.

- FDA has issued a regulation that describes its interpretation* of the term “protein” in the amended statutory definition of “biological product”: Any alpha amino acid polymer with a specific, defined sequence that is greater than 40 amino acids in size

- On March 23, 2020, an approved NDA for a “biological product” was deemed to be an approved 351(a) BLA for the biological product in accordance with the BPCI Act

- Once this transition occurred, applicants could seek licensure under section 351(k) of products that are biosimilar to, or interchangeable with, transitioned reference products

* Definition of the Term “Biological Product”, Final Rule February 21, 2020 (85 FR 10057)

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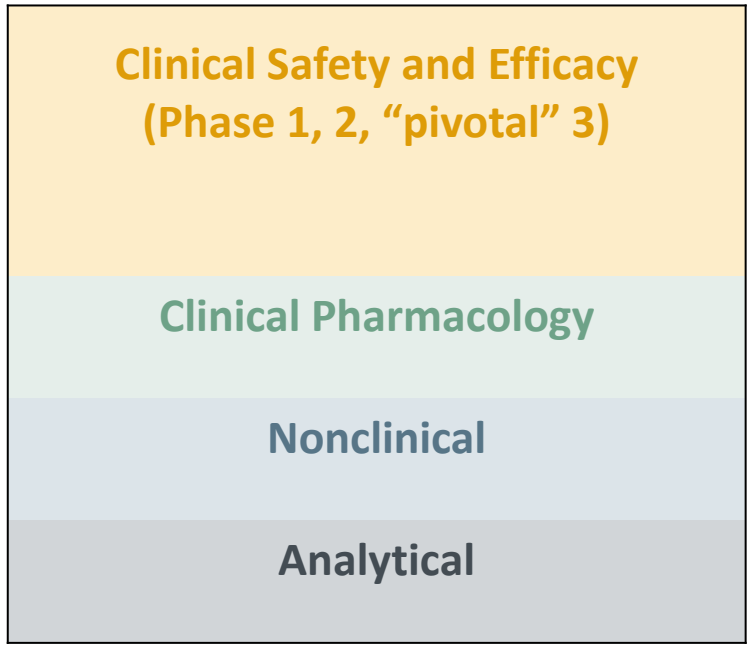
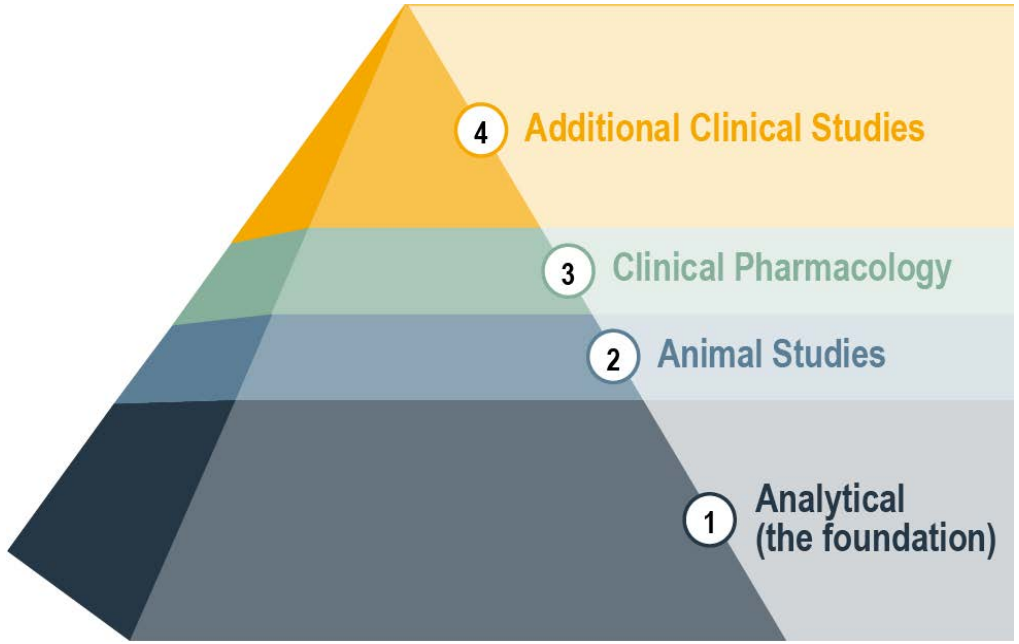
FDA's Approach to the Development of Biosimilars and a Case Study

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

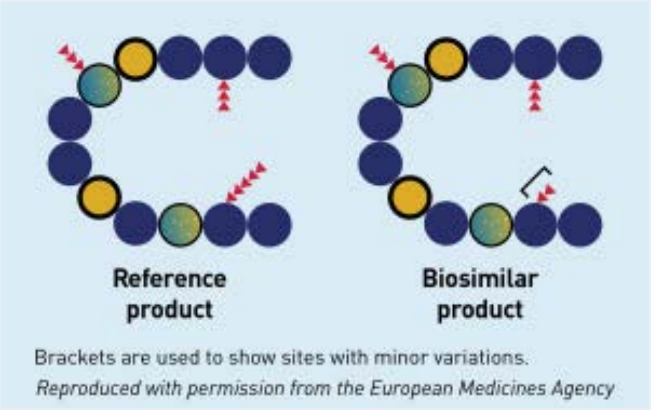


"Abbreviated": 351(k) BLA
Goal: To demonstrate biosimilarity (or interchangeability) to a reference product



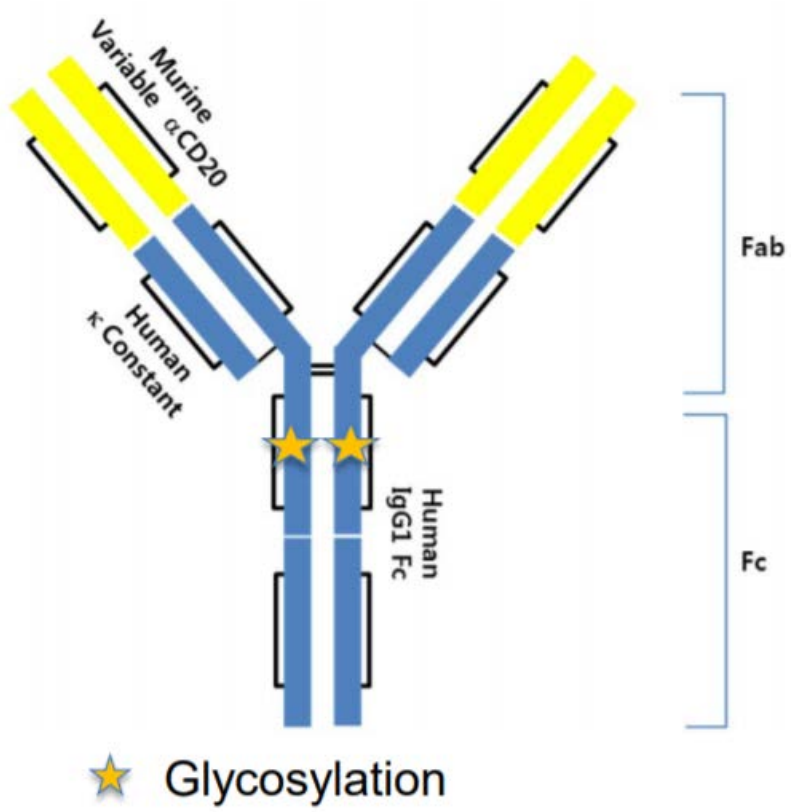
What does this difference mean from a development perspective?

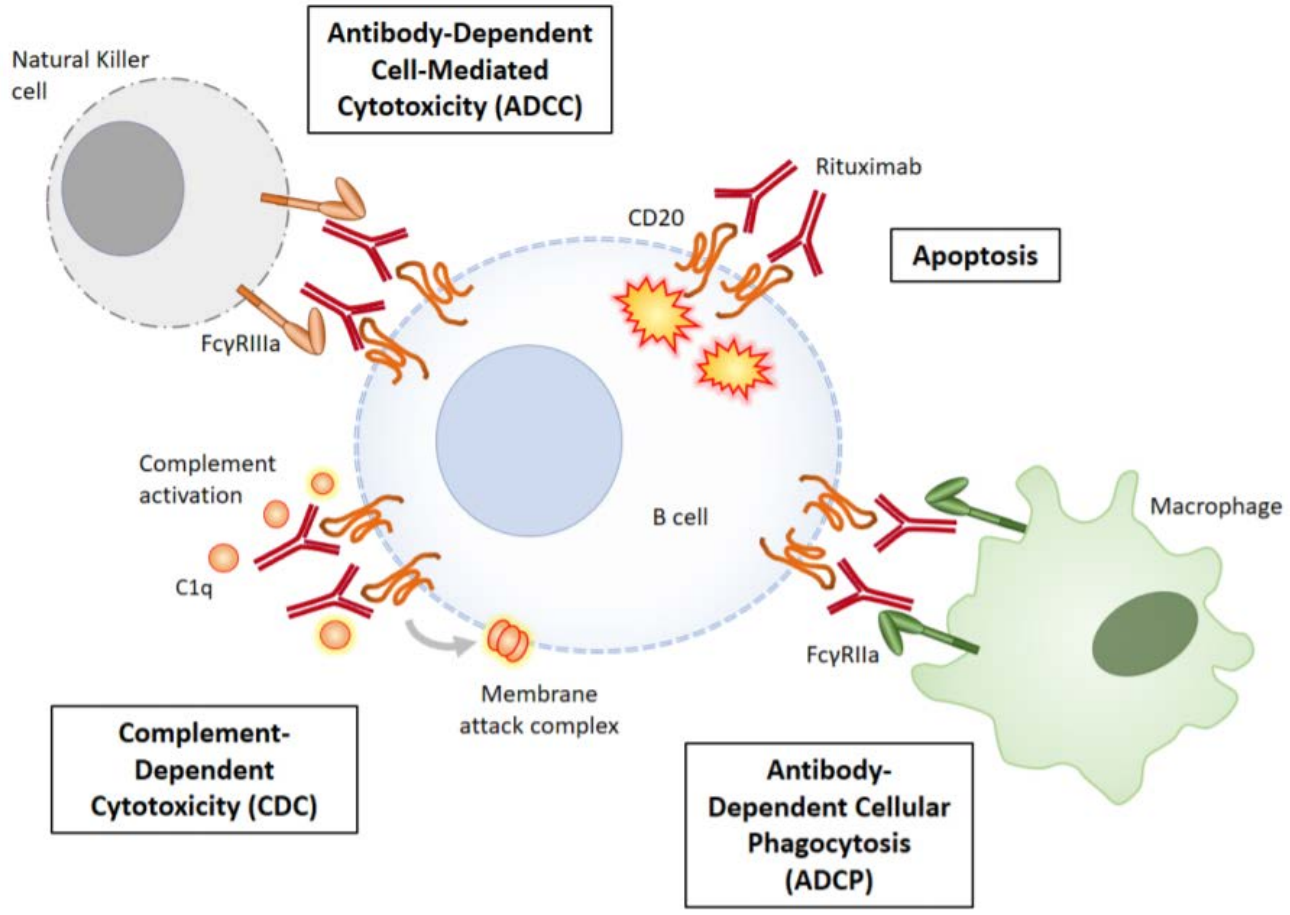
Generic vs. Biosimilar

	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		
Clinical Pharmacology Studies	Demonstrate PK Bioequivalence	Demonstrate PK/PD similarity, 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.

Case study of Data Used to Support Biosimilarity





CT-P10, proposed biosimilar to US-Rituximab

Adapted from 10/10/18 FDA Oncology Drugs Advisory Committee (ODAC) Slides

Case study of Analytical Data Used to Support Biosimilarity
Quality Attributes Evaluated

Primary structure

- Intact molecular weight
- Amino acid sequence
- Extinction coefficient

Higher order structure

- Secondary structure
- Tertiary structure
- Thermal stability
- Disulfide bonds

Glycosylation

- Afucosylation
- Galactosylation
- High Mannose content
- Sialylation

Biological activity

- CDC
- ADCC
- ADCP
- Apoptosis

- CD20 binding
- C1q binding
- FcγRIIIa V type binding
- FcγRIIIa F type binding
- FcγRIIIb binding
- FcγRIIa binding
- FcγRIIb binding
- FcγRI binding
- FcRn binding

Protein Concentration

- Concentration in mass per volume

Size Variants

- Monomer, dimer, high and low molecular weight species
- Intact IgG, “non-assembled forms” of heavy chain and light chain, fragments

Charge Variants

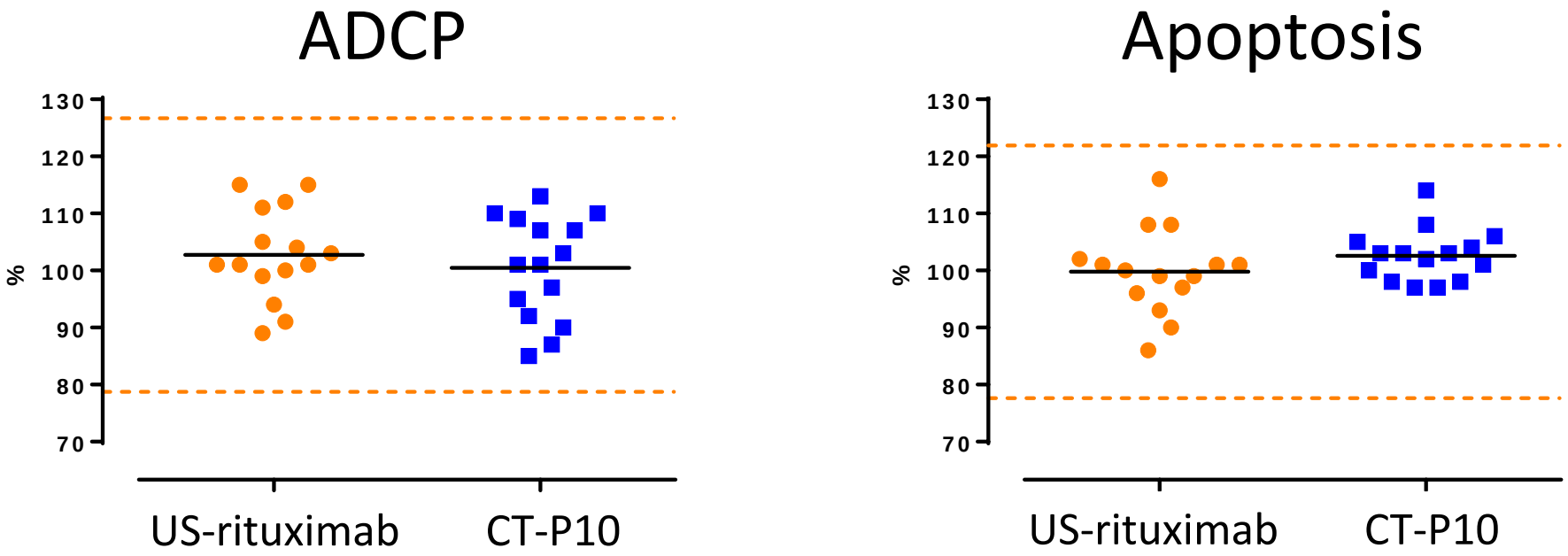
- Acidic, main, basic species

Post-translational Modifications

- Deamidation, Oxidation, Glycation, N- and C-terminal variants

Adapted from 10/10/18 FDA ODAC Slides

Case study – Potency Example



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

The relative ADCP and apoptotic activities of all CT-P10 lots are within the Quality Range (QR) limits of US-rituximab lots.

Adapted from 10/10/18 FDA ODAC Slides

Case study – Overall Conclusions From the Comparative Analytical Assessment

- The comparative analytical data demonstrate that CT-P10 is highly similar to US-rituximab notwithstanding minor differences in clinically inactive components.

- The analytical results add to the totality of the evidence to support a demonstration of biosimilarity between CT-P10 and US-rituximab.

Adapted from 10/10/18 FDA ODAC Slides

Comparative Human PK and PD Data

- PK and/or PD is generally considered the most sensitive clinical study/assay in which to assess for differences between products, should they exist

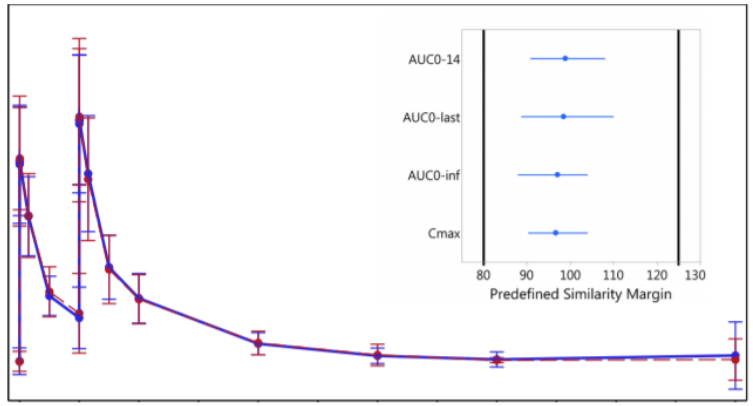
- PK
  - Demonstrate **PK similarity** in an adequately sensitive population to detect any differences, should they exist
- PD
  - **Similar PD** using PD measure(s) that reflects the mechanism of action (MOA) or reflects the biological effect(s) of the drug

- Clinical PK data generally will be expected; PD data desirable (case by case)

- **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)

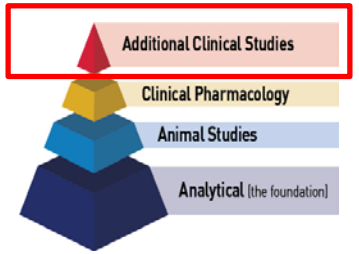
Case study – PK Similarity Study

- Parallel-group study, two doses, 1000 mg IV administration in patients with Rheumatoid Arthritis (RA)
- PK parameters – $AUC_{0\text{-inf}}$, $AUC_{0\text{-last}}$, $AUC_{0\text{-14d}}$, and C_{max}
- The geometric mean ratios and 90% CIs are within the pre-specified 0.80-1.25 range
- PK study results support a demonstration of no clinically meaningful differences and add to the totality of evidence to support a demonstration of biosimilarity



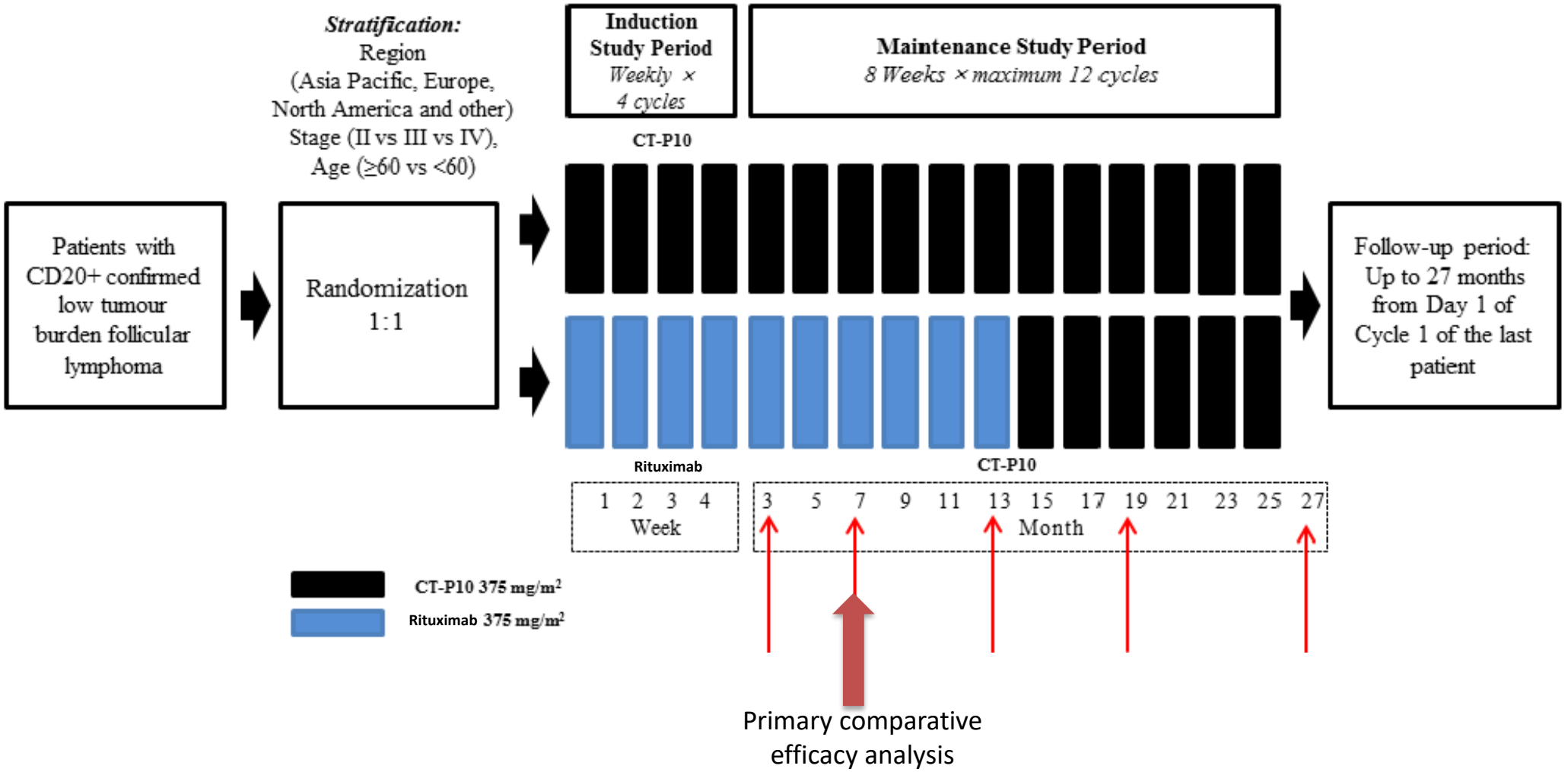
Adapted from 10/10/18 FDA ODAC Slides and Briefing Document

Comparative Clinical Study



- When a comparative clinical study is needed it should use endpoints that can assess **clinically meaningful differences** between the proposed product and the reference product
- Population, endpoint, sample size and study duration should be **adequately sensitive to detect differences**, should they exist
- Generally, a study is designed to establish statistical evidence the proposed product is neither inferior nor superior. Typically, an equivalence design would be used, but other designs may be justified
- Assessment of safety and immunogenicity is expected

Case study – Clinical Study in Subjects with Low Tumor Burden Follicular Lymphoma



Source: 10/10/18 FDA ODAC Briefing Document

Abbreviations: CD20+, cluster of differentiation 20 positive; CT, computed tomography

Case study – Clinical Study Endpoints and Margin Selection

- Primary endpoint: overall response rate (ORR) at 7 months
- Margin Selection of ± 17%
  - Treatment effect estimated from historical data (public knowledge)
  - Margin designed to preserve 77% of the rituximab treatment effect
- Test for Equivalence
- The 90% CI was within the equivalence margin (-17%, +17%)

	CT-P10 (N = 130)	US-Rituximab (N = 128)
Overall Response, n (%)	108 (83.1)	104 (81.3)
ORR Difference, (90% CI)	1.8 (-6.2, 10.0)	

Adapted from 10/10/18 FDA ODAC Briefing Document

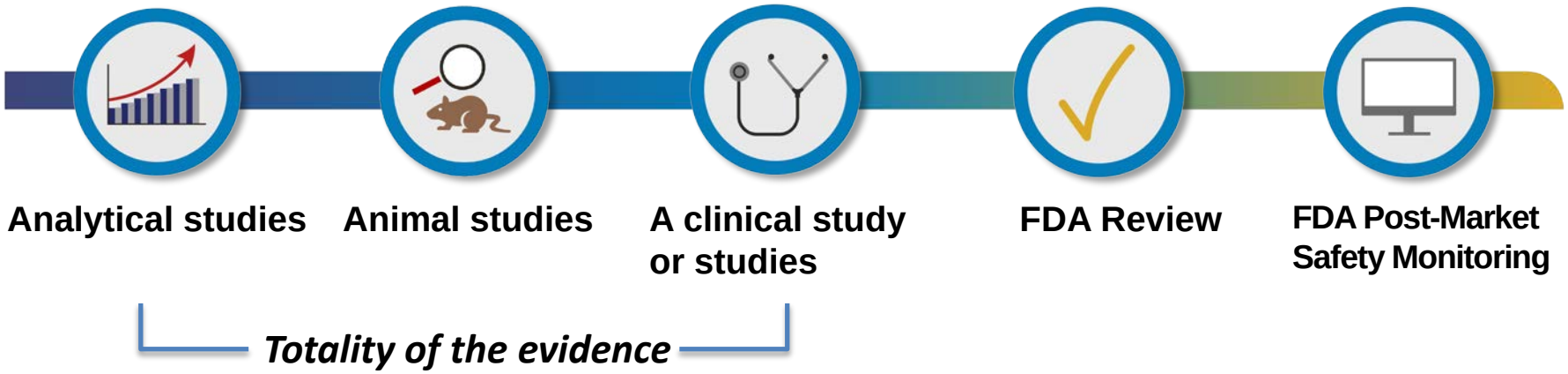
Case Study - Summary

- Comparative analytical data demonstrate that CT-P10 and US-rituximab are highly similar, notwithstanding minor differences in clinically inactive components
- PK and immunogenicity data in patients with RA support the demonstration of no clinically meaningful differences
- Clinical data obtained in patients with LTBFL and AFL support a demonstration that there are no clinically meaningful differences between CT-P10 and US-rituximab
- The totality of the data support the Applicant's claim that CT-P10 is biosimilar to US-licensed rituximab

Adapted from 10/10/18 FDA ODAC Slides

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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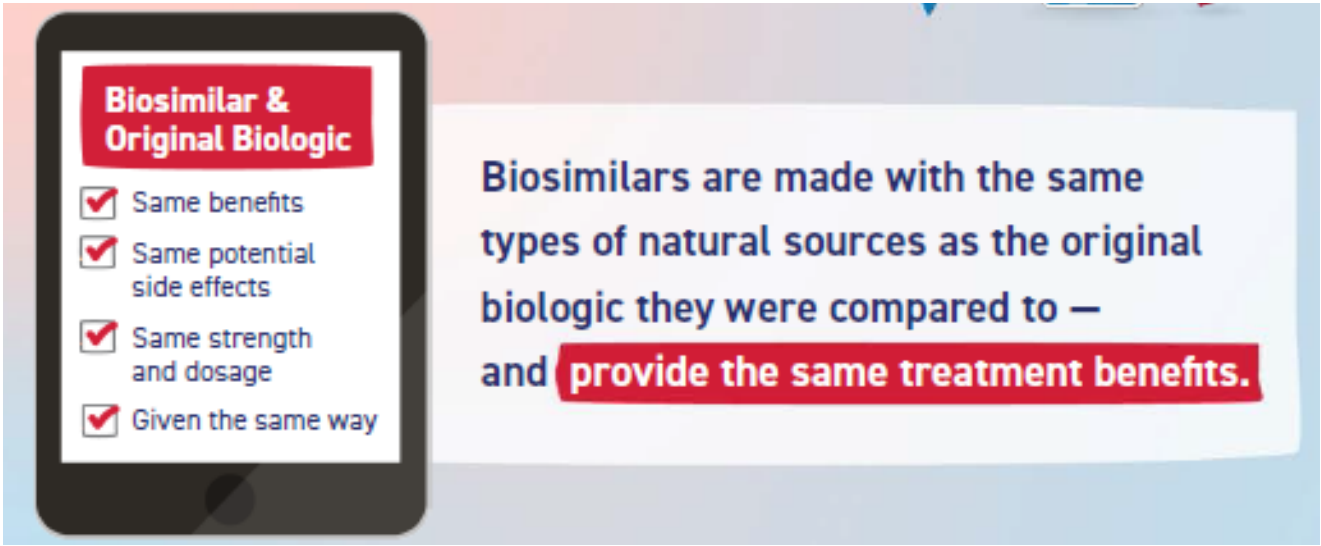
Using Biosimilar and Interchangeable Products

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.

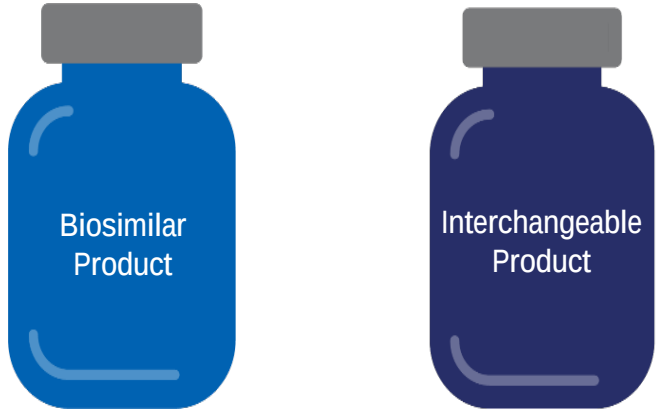
- Once available in the U.S., states may permit a pharmacist to substitute an interchangeable product for the reference product without consulting the prescriber.



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 example it may be licensed for a subset of indications
  - FDA recommends that biosimilar product labeling incorporate relevant data and information from the FDA approved labeling for the reference product, along with any appropriate modifications specific to the biosimilar product
  - **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: Differences between the biosimilar and reference product may be expected due to both products' molecular complexity, but such differences are not clinically meaningful.

Fact: Biosimilar 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.

Fact: FDA's approval of an interchangeable biological product does not indicate a higher standard of biosimilarity, 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 "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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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

BAP in Review (cont.)

Completed Activities

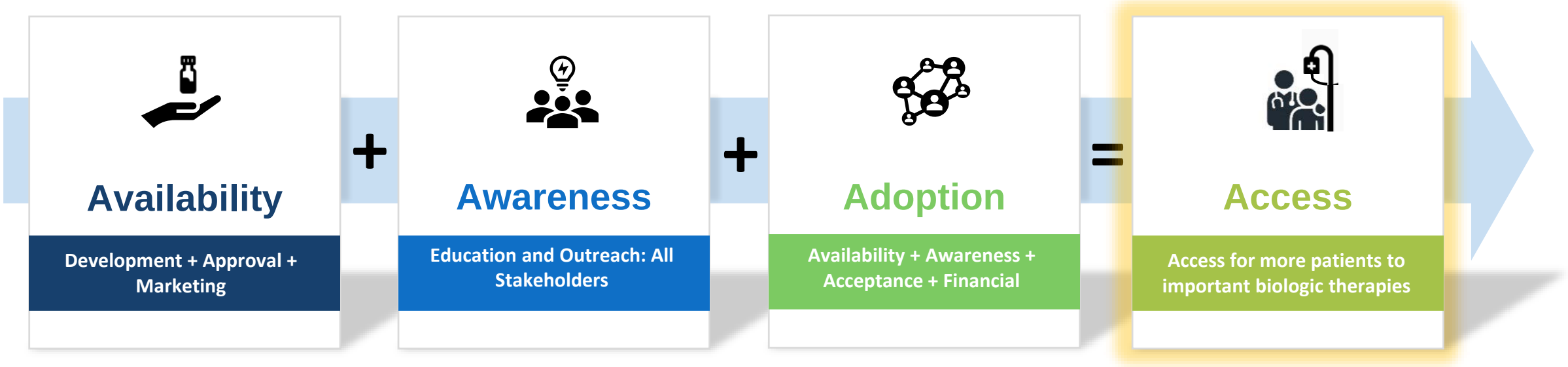
- Held Public Meeting on Insulin Products
- Released Draft Guidance, "Promotional Labeling and Advertising Considerations for Reference and Biosimilar Products – Q & A"
- Released "Biosimilar Basics" for patients including materials in Spanish
- Released Draft Guidance, "Licensure for Fewer Than All Conditions of Use"
- Released Draft Guidance, "Biosimilarity and Interchangeability: Additional Q & A"
- Stakeholder Meetings
- Held Public Hearing between FTC and FDA
- Released Draft Guidance, "Clinical Immunogenicity of Biosimilar and Interchangeable Insulin Products"
- Other Engagement Activities

Key In-Progress Activities

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

Supporting a competitive marketplace

Solving The Equation for Patient Access



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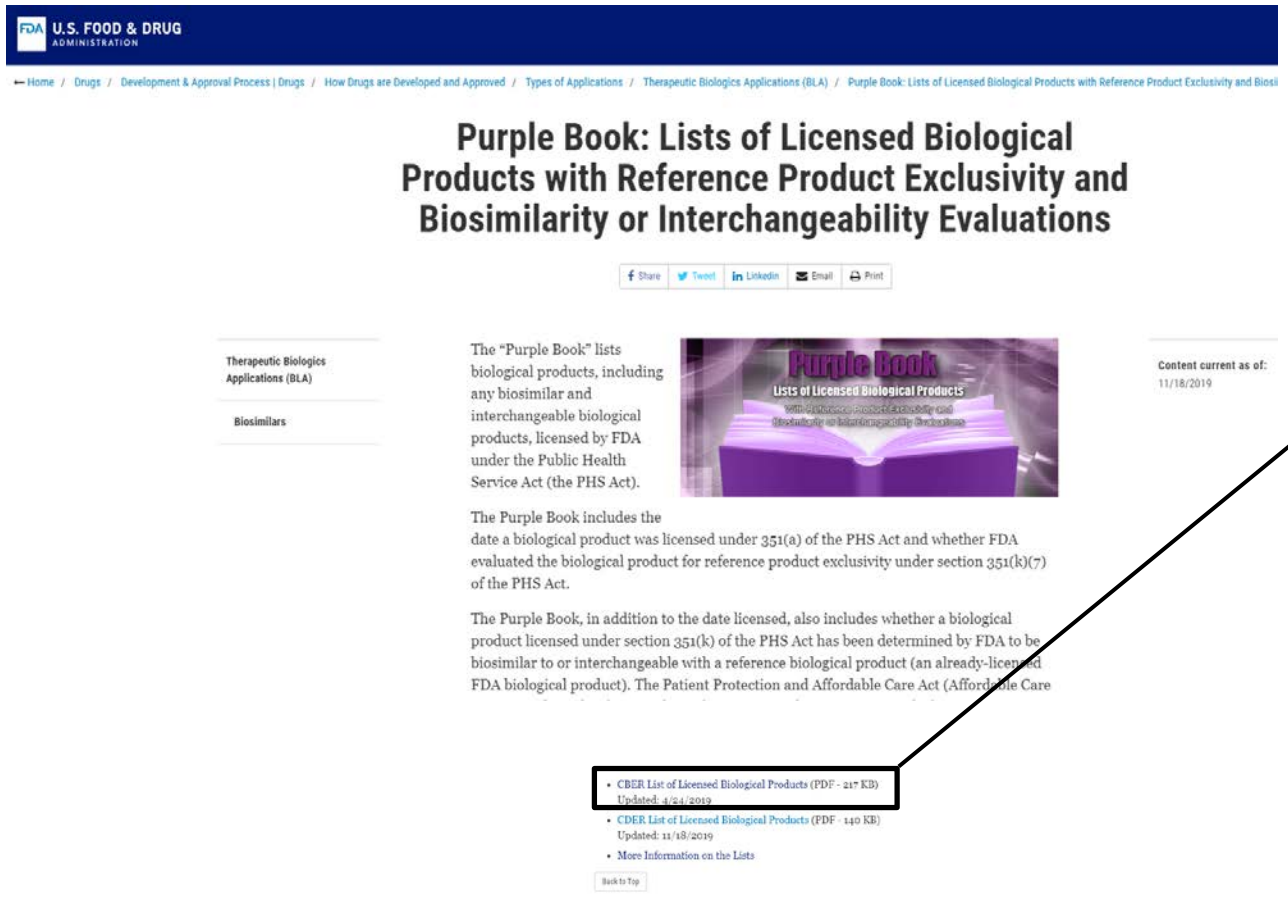
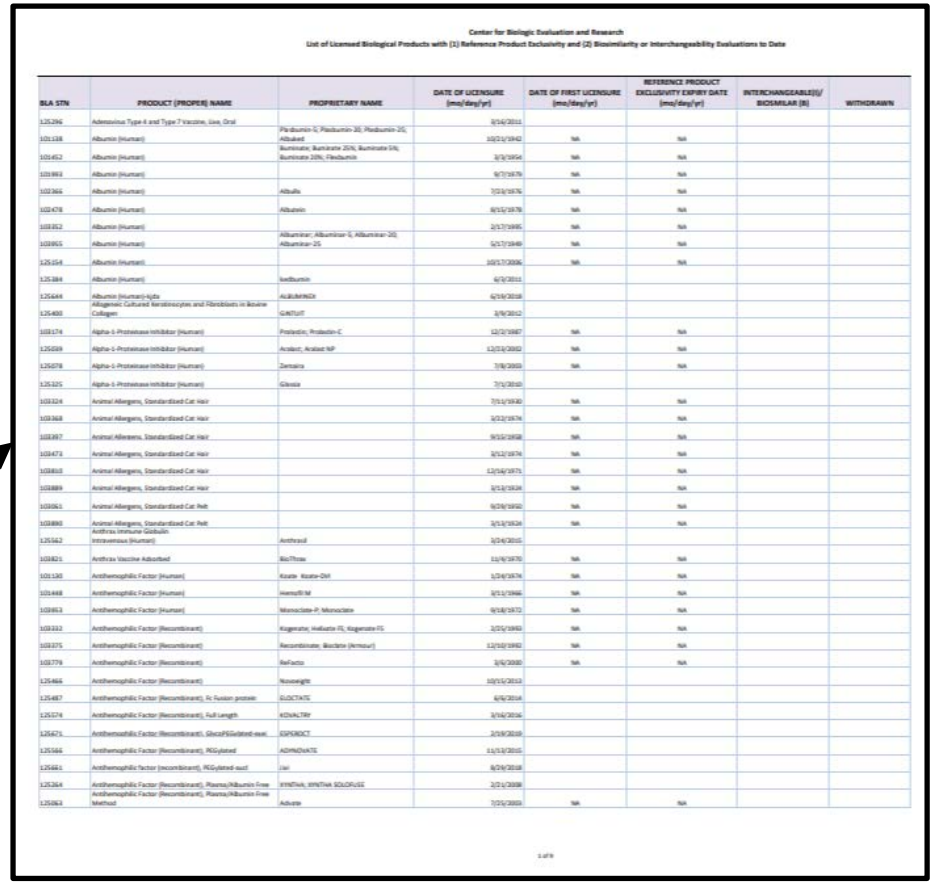
Resources for Health Care Providers

Purple Book

The Purple Book is available as a PDF format on FDA.gov.





The Purple Book Database

The new Purple Book can be found at PurpleBookSearch.fda.gov .

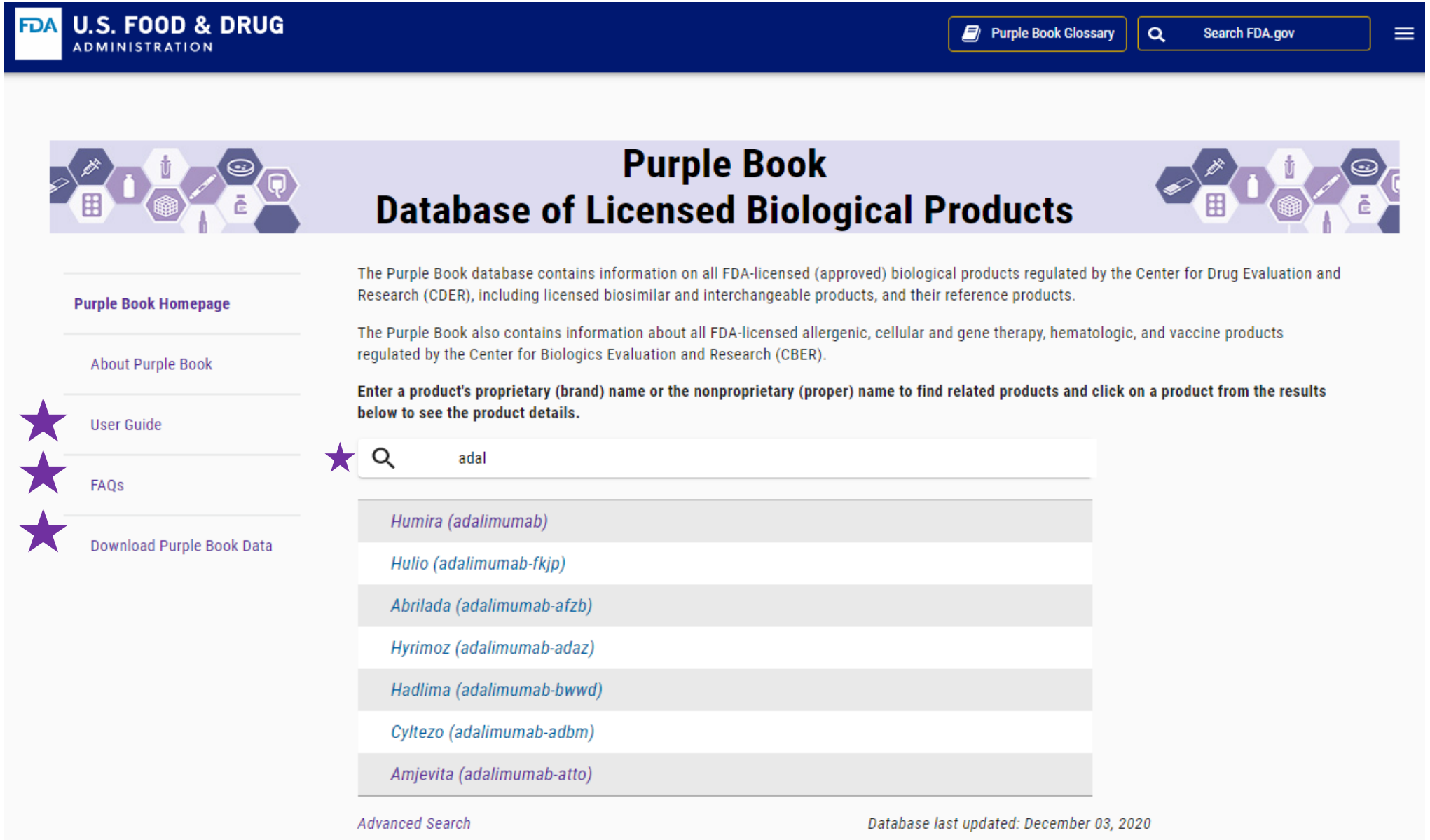
Purple Book's New Features

The new database provides patients, payors, clinicians, and others with an accessible, easy-to-use online search engine with more information about FDA-approved biological products, including biosimilar and interchangeable biological products.

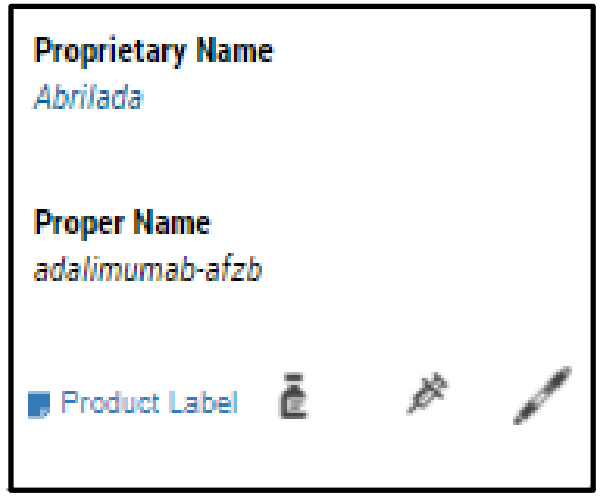
The searchable database utilizes new features tailored to different user needs, including:

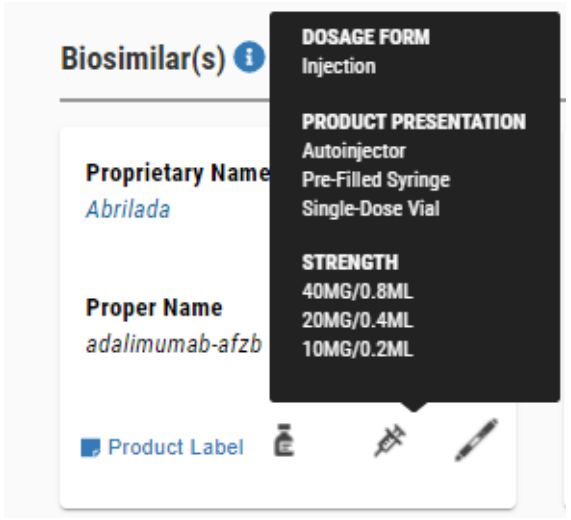
- Simple and Advanced Search options
- Auto-suggest search function
- Additional search filters
- Data download options
- Links to product labels
- Ability to show/hide sortable columns of information
- Ability to print or export search results
- Searchable glossary of terms

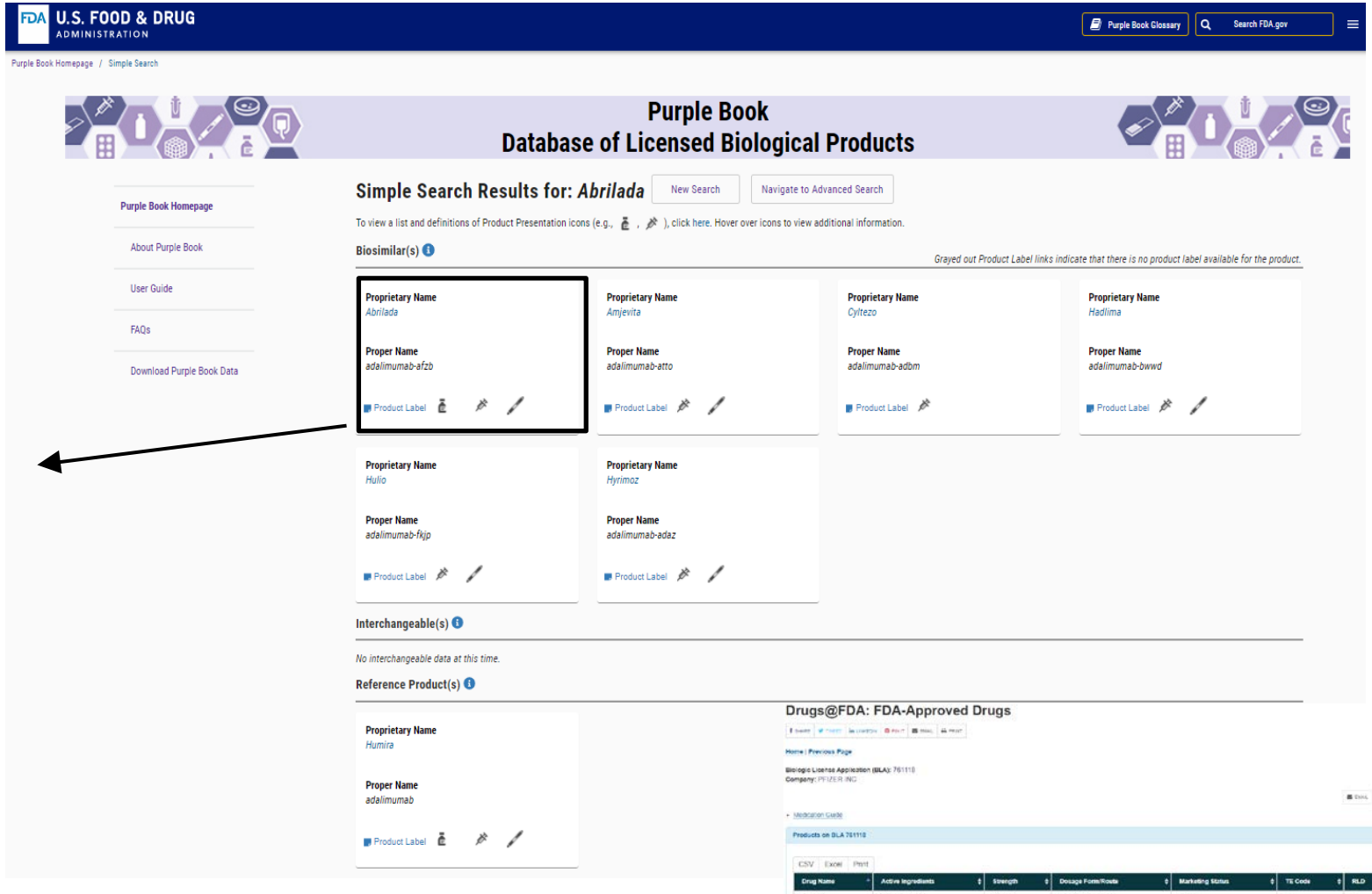
Simple Search

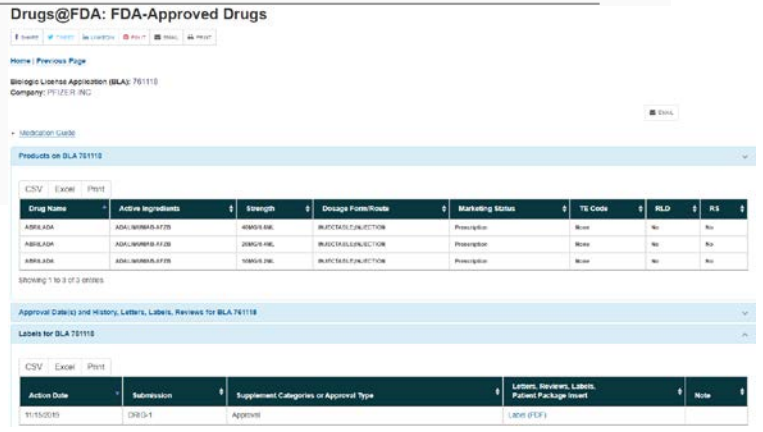


Product Label Information

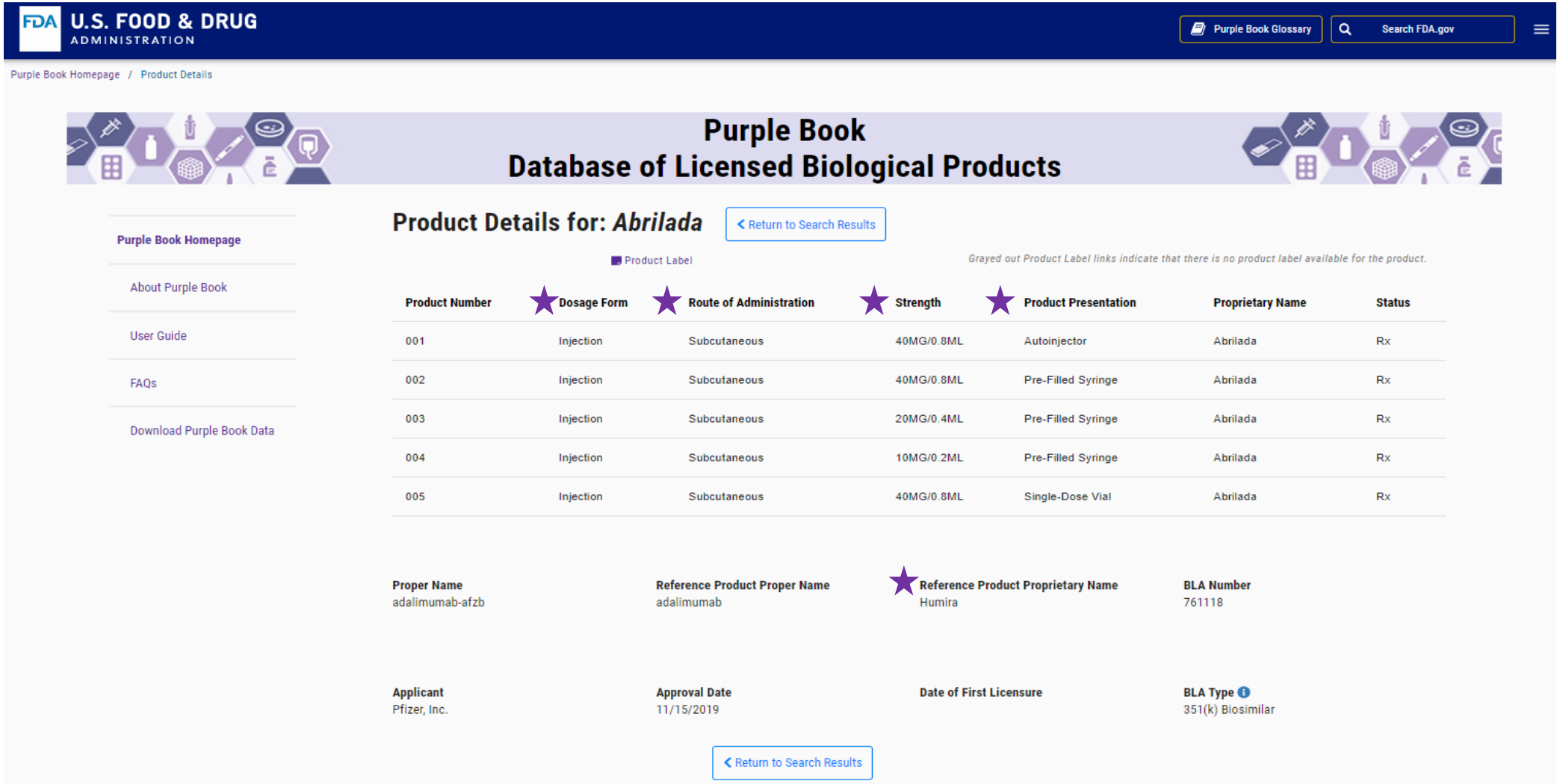




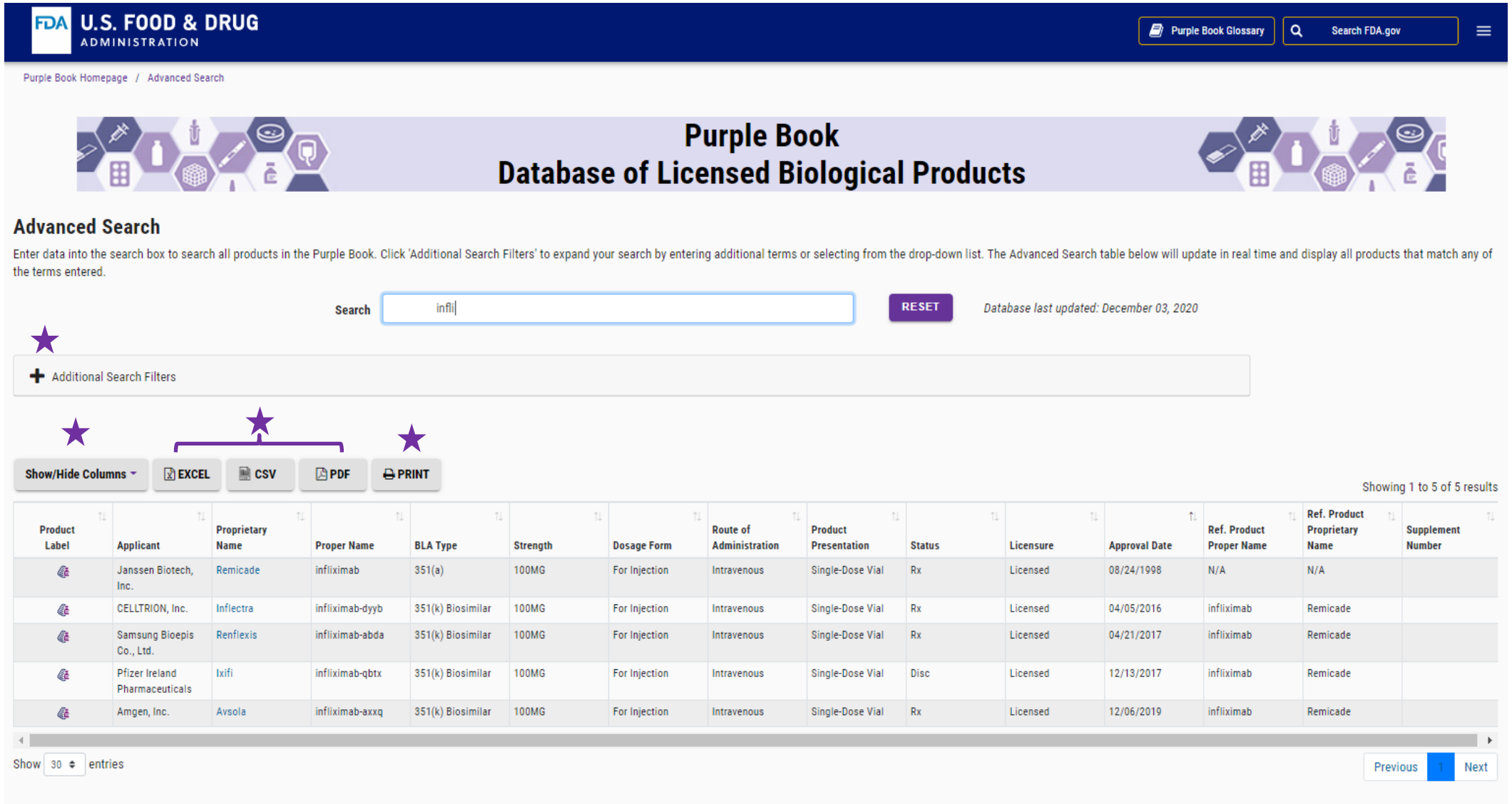




Product Details Page

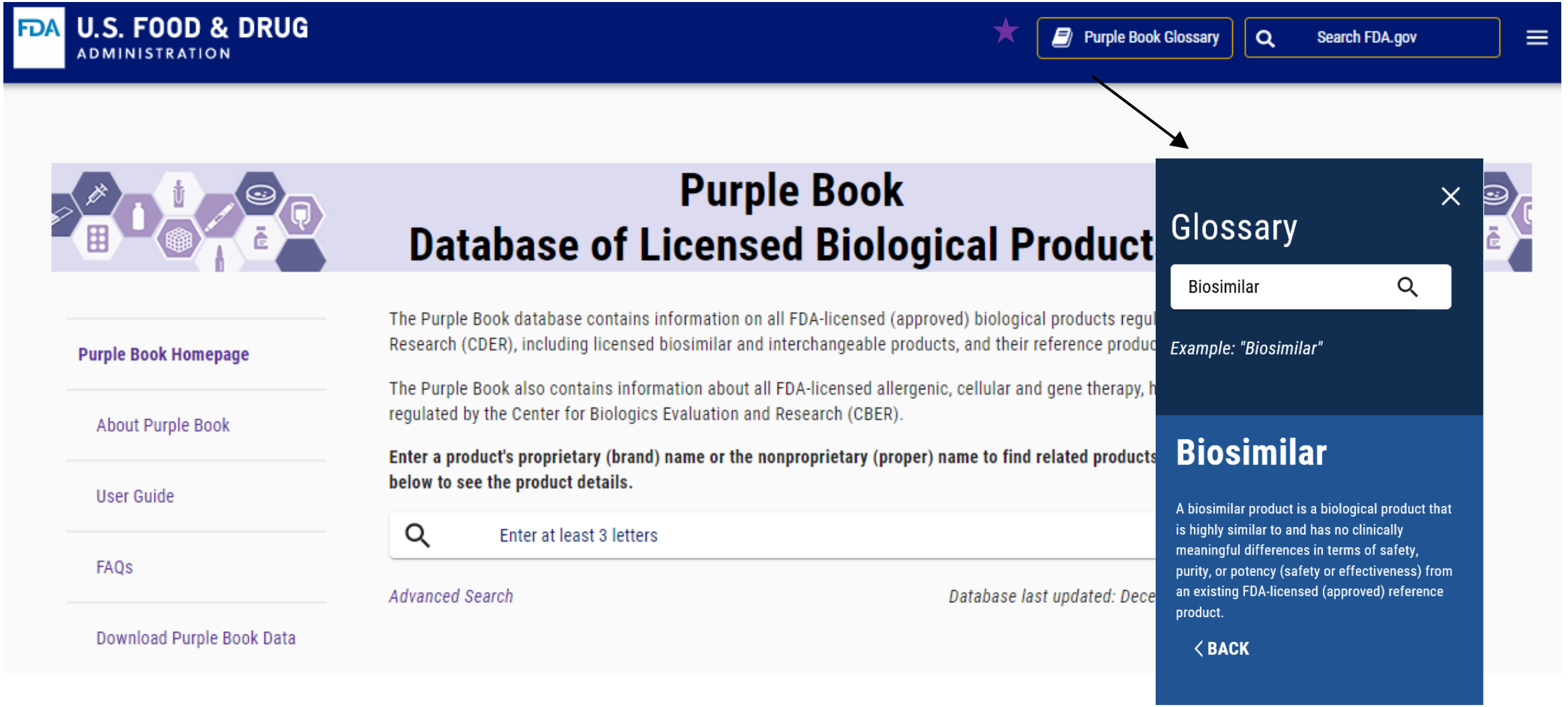


Advanced Search



Product Label	Applicant	Proprietary Name	Proper Name	BLA Type	Strength	Dosage Form	Route of Administration	Product Presentation	Status	Licensure	Approval Date	Ref. Product Proper Name	Ref. Product Proprietary Name	Supplement Number
	Janssen Biotech, Inc.	Remicade	infliximab	351(a)	100MG	For Injection	Intravenous	Single-Dose Vial	Rx	Licensed	08/24/1998	N/A	N/A	
	CELLTRION, Inc.	Inflectra	infliximab-dyyb	351(k) Biosimilar	100MG	For Injection	Intravenous	Single-Dose Vial	Rx	Licensed	04/05/2016	infliximab	Remicade	
	Samsung Bioepis Co., Ltd.	Renflexis	infliximab-abda	351(k) Biosimilar	100MG	For Injection	Intravenous	Single-Dose Vial	Rx	Licensed	04/21/2017	infliximab	Remicade	
	Pfizer Ireland Pharmaceuticals	Ixifi	infliximab-qbtx	351(k) Biosimilar	100MG	For Injection	Intravenous	Single-Dose Vial	Disc	Licensed	12/13/2017	infliximab	Remicade	
	Amgen, Inc.	Avsola	infliximab-axxq	351(k) Biosimilar	100MG	For Injection	Intravenous	Single-Dose Vial	Rx	Licensed	12/06/2019	infliximab	Remicade	

Glossary of Terms

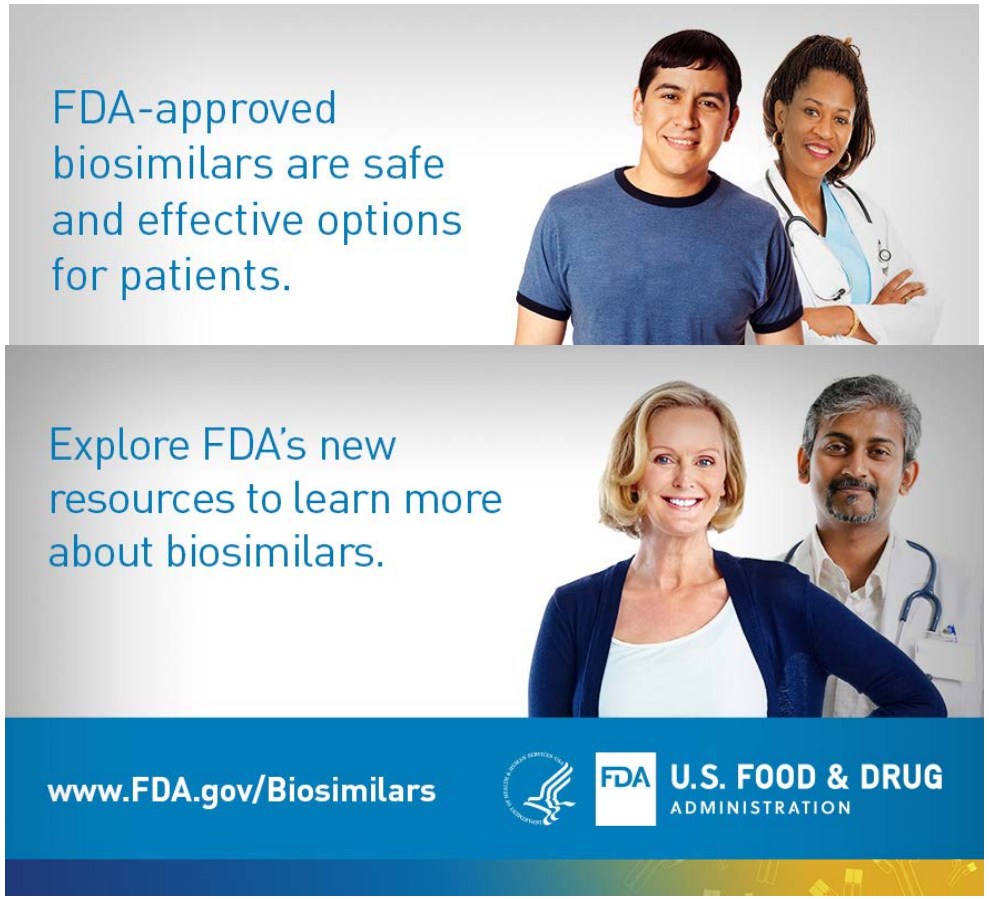


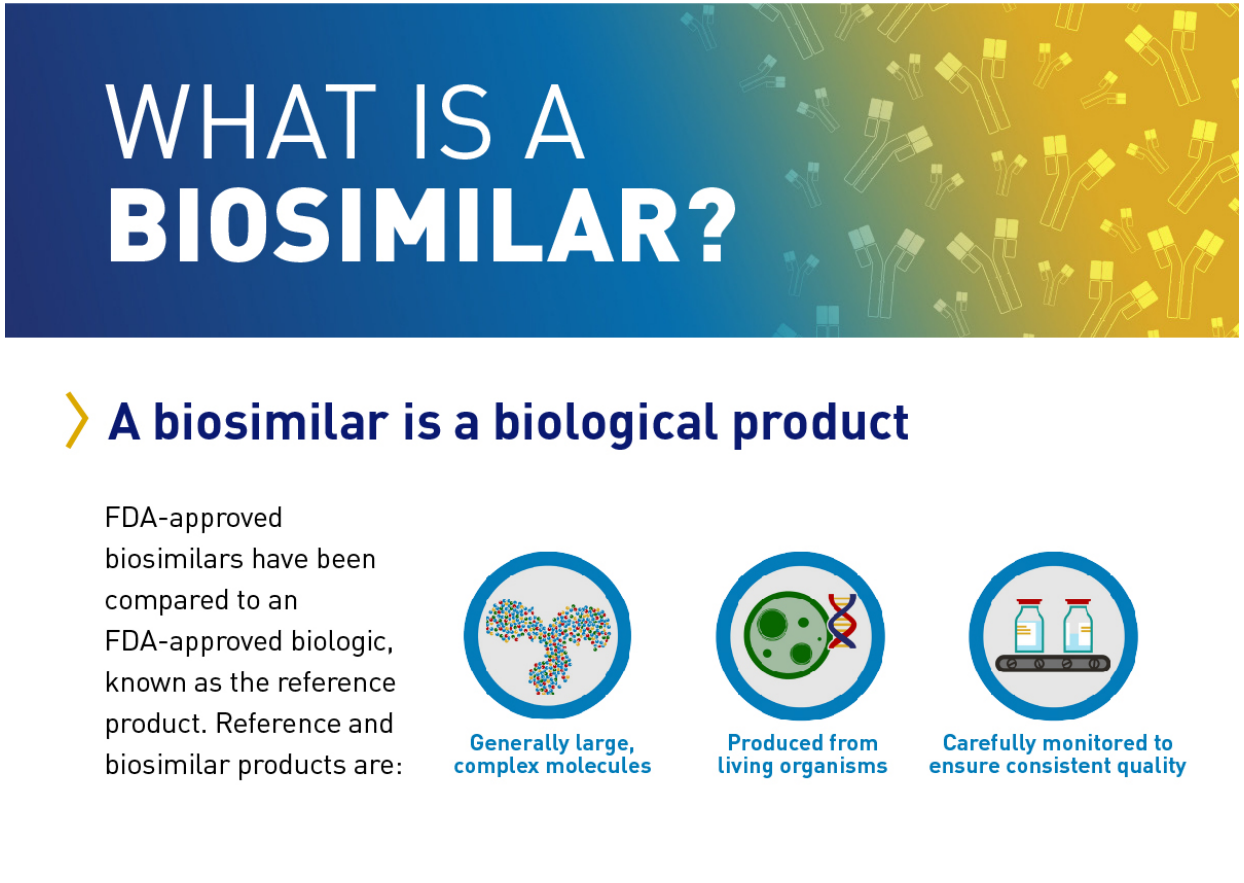
Education and Outreach

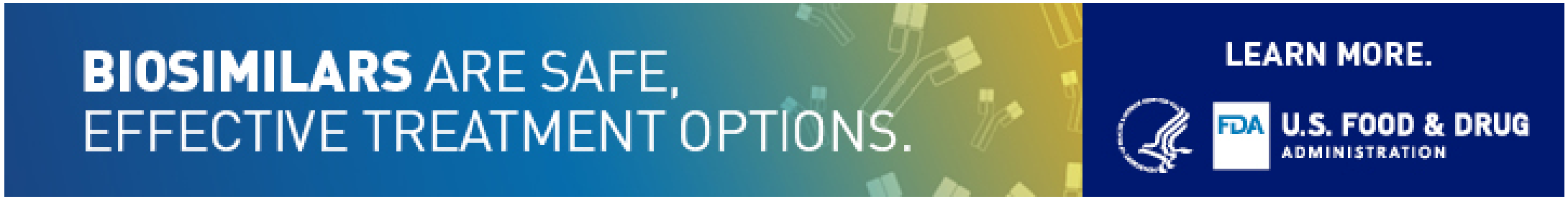
- FDA is committed to developing effective communications to improve understanding of biosimilars among patients, health care providers and payors
  - **Engaging** with health care professional and patient stakeholders
  - **Developing** educational materials for health care prescribers, pharmacists,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

FDA is committed to fulfilling their important role as one of many stakeholders

Health Care Provider Materials







Web Content and Infographic:

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

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

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:
  - Fact Sheets and Videos
  - 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 CDER 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. Cohen, H.P., Blauvelt, A., Rifkin, R.M. et al. “Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes.” Drugs 78, 463–478 (2018). https://doi.org/10.1007/s40265-018-0881-y
4. Datta-Mannan. “ Mechanisms Influencing the Pharmacokinetics and Disposition of Monoclonal Antibodies and Peptides.” *CPT Pharmacometrics Syst Pharmacol*. 2017;6(9):576-588. doi:10.1002/psp4.12224
5. Walsh, G. “Biopharmaceutical benchmarks 2018.” Nat Biotechnol 36, 1136–1145 (2018). https://doi.org/10.1038/nbt.4305
6. Guidance for Industry: Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products. November 2019. https://www.fda.gov/media/133014/download
7. Oncology Drugs Advisory Committee meeting on October 10, 2018. Meeting materials: https://www.fda.gov/advisory-committees/advisory-committee-calendar/meeting-oncologic-drugs-advisory-committee-10102018-10102018#event-materials

Questions?

Thank You

www.fda.gov/biosimilars