Biocon Biologics

Biosimilar Interchangeability in Context

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Enabling Affordable Access to Lifesaving Biosimilars, Worldwide

Interchangeability Historical Perspective

2010: BPCIA grants FDA authority to approve a biosimilar IC Products

- BPCIA modeled after Hatch-Waxman Act: Approval process for generics
  - To encourage competition & promote innovation in the field of biologics.
- Separate IC designation: Based on theory of increased immunogenicity
  - By switching from reference to the biosimilar could change the safety, efficacy or potency of the biologic due to immunogenicity reaction.
  - Needed additional data beyond biosimilarity to obtain IC designation
- State Level: Permitted the substitution of a reference product for an interchangeable biosimilar without the approval of the prescribing physician.
  - substituted for the reference product at a pharmacy

2019 Interchangeability Guidance

How residual uncertainty has evolved and "additional data requirements"

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- Demonstrate Biosimilarity
- Provide Data to meet 351(k)(4)(A): Standard may vary depending on the interchangeable
  - Critical Quality Attributes
  - Product Complexity and the Extent of Comparative and Functional Characterization
  - Analytical differences: reference vs proposed interchangeable, & potential clinical impact of differences
  - Analyze each condition of use the reference product is licensed, & different patient populations
    - Mechanism of Action
    - Expected PK and biodistribution of the product Expected differences in the expected immunogenicity risk
    - Expected toxicities
- Demonstrate that switching between 2 products would not increase safety or decrease efficacy

  May be done by a clinical switching study:
  - Purpose: To demonstrate that there is no change in efficacy or safety after 3 switches between the proposed interchangeable biosimilar and the reference product.
- Post marketing surveillance data from the licensed biosimilar product in addition to data from an appropriately designed switching study may be needed to address uncertainty

If a sponsor of a proposed interchangeable product believes **that data from a switching study is not necessary, FDA expects the sponsor to provide a justification for not needing** such data as a part of the demonstration of interchangeability

Impact of IC Designation: One consequence was confusion

Only HA in the world with a separate designation,
Is an interchangeable Biosimilar safer, better quality?
"Higher standards of Approval?"

- 2024: Confusion in the market, medical community and payers still exists:
- Biosimilar's council : "Misinformation Undermines the Perception of Safety and Efficacy of Biosimilars" Friday July 26, 2024
    - *However, misinformation campaigns – often driven or silently funded by brand manufacturers – have sought to limit adoption of these U.S. Food and Drug Administration (FDA)-approved products. These campaigns are intended to sow doubt among patients and prescribers regarding biosimilars' safety and efficacy, and to construct regulatory, policy and legal roadblocks to competition. This helps explain why, as of 2023, the average market share for biosimilars was barely 20 percent.[2]*

- However, FDA has always stated: Both biosimilars and interchangeable biosimilars must meet the same high standard of biosimilarity for FDA approval
    - Both are as safe and effective as the reference product.

- Since 2010: Experience and technology has led to the evolution of interchangeable biosimilars requirements
    - 1st approved a biosimilar 2015,
    - April 2024 : 48 Biosimilars are approved, 15 different biologic products
    - Large FDA PV database

IC Designation Requirements have an impact

Goal: Achieve Low residual uncertainty through other means than Switching trials

- Clinical Switching Studies impact precious resources if they are not scientifically grounded
  - Patients enrolled in IC study could be better served in other clinical research
  - Impact on the medical community: Physicians, staff, hospital beds, time etc
  - Added cost translate to higher prices for patients
- Misinformation: confusion for patients, medical community, state level, payer community that an IC has higher quality.
- It did not only impact Pharmacist Decision
  - Lower uptake: Pharmacists required biosimilar specific Rx unless an IC
  - Hospitals easier to just accept IC products based on perceived differences
  - Patient's education, inconvenience, unaware a lower costs alternative were available

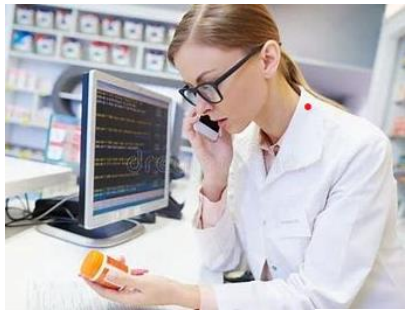
- Available technology to predict immunogenicity via can achieve low residual uncertainty
  - Analytics (including physical, chemical and biological function assays),
  - pharmacological and clinical correlations as relates to interchangeability

Why is the IC designation important for patients, caretakers, prescribers and Physicians

Patient receives prescription for the Branded Reference Biologic?

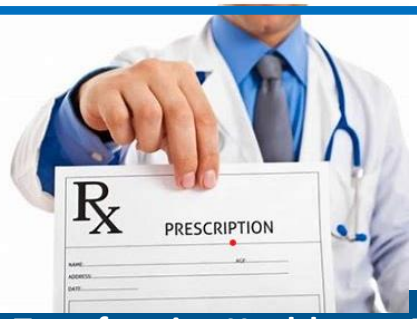
Patient goes to get the prescription filled
Learns there is a biosimilar available that is more affordable with the same quality, safety and efficacy profile.

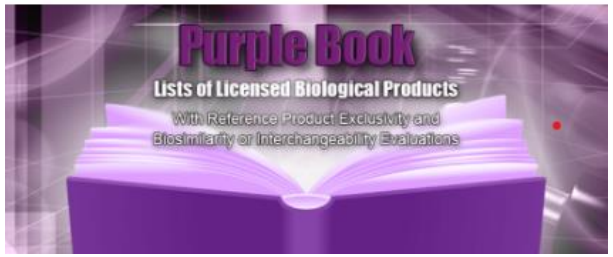
- Doesn't have a Rx for the biosimilar



To receive the biosimilar the Pharmacist will have to locate the physician and obtain a new prescription

An IC biosimilar can be substituted for the reference product at a pharmacy without intervention from the physician





FDA
Purple book

Database of Licensed Biological Products

What does the Pharmacist see?

Does your medication have an approved biosimilar.

No Product with IC designation

Biosimilar(s)

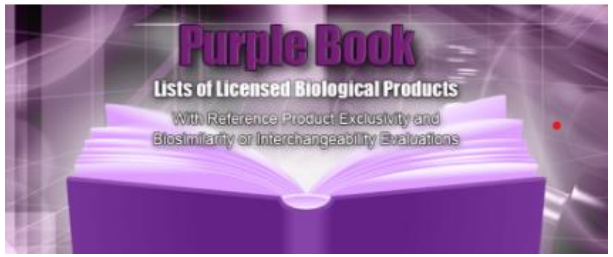
Proprietary Name	Proper Name	
Riabni	*rituximab-arrx*	PRODUCT LABEL
Ruxience	*rituximab-pvvr*	PRODUCT LABEL
Truxima	*rituximab-abbs*	PRODUCT LABEL

Interchangeable(s)

No interchangeable data at this time.

Reference Product(s)

Proprietary Name	Proper Name	
Rituxan	*rituximab*	PRODUCT LABEL
Rituxan	*rituximab*	PRODUCT LABEL
Rituxan Hycela	*rituximab and hyaluronidase human*	PRODUCT LABEL



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Database of Licensed Biological Products

What does the Pharmacist see?

Does your medication have an approved biosimilar.

Product with IC designation

Biosimilar(s)

Proprietary Name
Pyzchiva

Proper Name
ustekinumab-ttwe

PRODUCT LABEL

Proprietary Name
Pyzchiva

Proper Name
ustekinumab-ttwe

PRODUCT LABEL

Proprietary Name
Selarsdi

Proper Name
ustekinumab-aekn

PRODUCT LABEL

Interchangeable(s)

Proprietary Name
Wezlana

Proper Name
ustekinumab-auub

PRODUCT LABEL

Proprietary Name
Wezlana

Proper Name
ustekinumab-auub

PRODUCT LABEL

Reference Product(s)

Proprietary Name
Stelara

Proper Name
ustekinumab

PRODUCT LABEL

Proprietary Name
Stelara

Proper Name
ustekinumab

PRODUCT LABEL

Start of the change:
BsUFA III User fee (FY 2023-2027):
Enhancing development Interchangeable Biosimilars & streamlined development of biosimilars

- **ENHANCING BIOSIMILAR AND INTERCHANGEABLE BIOLOGICAL PRODUCT DEVELOPMENT AND REGULATORY SCIENCE**
- FDA will develop foundational guidance's for the development of interchangeable biosimilars
  - By Sept, 2023: Draft guidance on labeling for interchangeable biosimilar biological products **completed**
  - By Sept 2024: Promotional labeling and advertising considerations for interchangeable biosimilar biological products **completed**
  - By Sept, 2025: Developing presentations, container closure systems & device constituent parts for interchangeable biosimilars
    - Important Device guidance
- Pilot a regulatory science program
  - Scientific Road Map: Goal to Achieve
    - Scientifically appropriate methodologies to predict immunogenicity by advancing the knowledge of analytical (including physical, chemical and biological function assays), pharmacological and clinical correlations as relates to interchangeability
    - Develop alternatives to and/or reduce the size of studies involving human subjects
    - In order to advance the development of interchangeable products and improve the efficiency of biosimilar development

Pilot a regulatory science program
Research Roadmap specifics to interchangeability

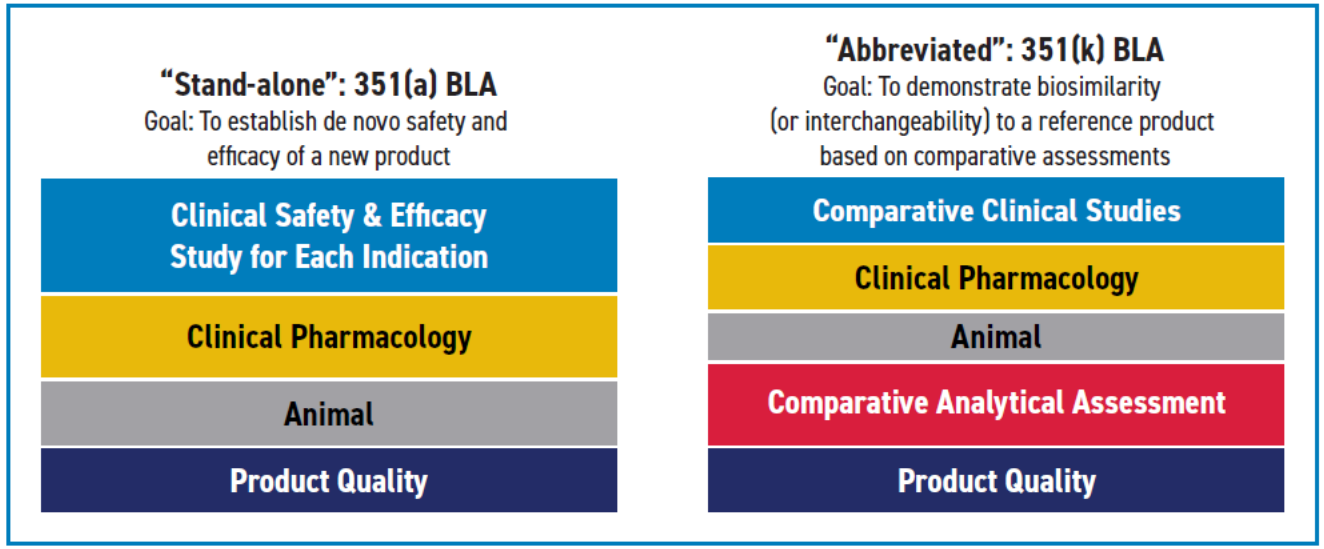

Figure 1. Typical data composition of a "Standalone" 351(a) Biologics License Application (BLA) and an "Abbreviated" 351(k) BLA

FDA: Biosimilar and interchangeable landscape will continue to evolve

- Focus on generation of information & methodologies to meet the safety standards for determining interchangeability under 351(k)4 of the PHS Act
- Highlights development of methodologies to predict immunogenicity
  - Advancing knowledge of analytical (including physical, chemical and biological function assays), pharmacological and clinical correlations as relates to interchangeability.

Knowledge since the 1st biosimilar has been approved

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Reference Products and Approved Biosimilars as of May 2024 (53 total) 10 Interchangeable

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Supportive Care

Epogen/Procrit
Retacrit (epoetin alfa-epbx)

Neulasta
Stimufend (pegfilgrastim-fpgk)
Fylnetra (pegfilgramstim-pbbk)
Nyvepria (pegfilgrastim-apgf)
Ziextenzo (pegfilgrastim-bmez)
Udenyca (pegfilgrastim-cbqv)
Fulphila (pegfilgrastim-jmdb)

Neupogen
Releuko (filgrastim-ayow)
Nivestym (filgrastim-aafi)
Zarxio (filgrastim-sndz)

Ophthalmology

Eylea
Opuviz* (aflibercept-yszy)
Yesafili* (aflibercept-jbzf)

Lucentis
Cimerli* (ranibizumab-eqrn)
Byooviz* (ranibizumab-nuna)

Osteoporosis

Prolia and Xgeva
Jubbonti and Wyost (denosumab-bbdz)

Oncology

Avastin
Avziri (bevacizumab-tnjn)
Vegzelma (bevacizumab-adcd)
Alymsys (bevacizumab-maly)
Zirabev (bevacizumab-bvzr)
Mvasi (bevacizumab-awwb)

Herceptin
Kanjinti (trastuzumab-anns)
Trazimera (trastuzumab-qyyp)
Ontruzant (trastuzumab-dttb)
Herzuma (trastuzumab-pkrb)
Ogivri (trastuzumab-dkst)
Hercessi (trastuzumab-strf)

Rituxan
Riabni (rituximab-arrx)
Ruxience (rituximab-pvvr)
Truxima (rituximab-abbs)

Autoimmune

Actemra
Tofidence (tocilizumab-bavi)
Tyenne (tocilizumab-aazg)

Enbrel
Eticovo (etanercept-ykro)
Erelzi (etanercept-szzs)

Humira
Yuflyma (adalimumab-aaty)
Idacio (adalimumab-aacf)
Yusimry (adalimumab-aqvh)
Hulio (adalimumab-fkjp)
Abrilada* (adalimumab-afzb)
Hadlima (adalimumab-bwwd)
Hyrimoz (adalimumab-adaz)
Cyltezo* (adalimumab-adbm)
Amjevita (adalimumab-atto)
Simlandi (adalimumab-ryvk)

Lantus
Rezvoglar* (insulin glargine-aglr)
Semglee* (insulin glargine-yfgn)

Remicade
Avsola (infliximab-axxq)
Ixifi (infliximad-qbtx)
Renflexis (infliximab-abda)
Inflectra (infliximab-dyyb)

Soliris
Bkmev* (eucalimzumab-aeeb)

Stelara
Wezlana* (ustekinumab-auub)
Selarsdi (ustekinumab-aekn)

Tysarbi
Tyruko (natalizumab-sztn)

Note: Products with an asterisk have the 351(k) Interchangeable designation.

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FDA updated Biosimilar labelling guidelines 2023

Same statement for Biosimilars and Interchangeable Biosimilars

- Previously, recommended that Prescribing Information (labeling) include a “Biosimilarity Statement” or “Interchangeability Statement” describing the product’s relationship to its reference product in the Highlights section
    1. NEXSYMEO (replicamab-cznm) **is biosimilar to** JUNEXANT (replicamab-hjxf).
    2. The interchangeability statement would be: NEXSYMEO (replicamab-cznm) **is interchangeable to JUNEXANT (replicamab-hjxf).**

- September 2023: FDA recommended all labeling for biosimilars, including interchangeable biosimilars, include one statement - a “biosimilarity statement”.
- Reasons:
    - Written for health care professionals. It’s primary purpose is to contain the essential scientific information needed for the safe and effective use of the product.
    - Not necessary for informing the safe and effective use of the product to prescribing health care professionals.
    - Information about interchangeability is relevant to substitution at the pharmacy.
    - Change for a variety of concerns, including increased confusion.
    - Interchangeability designation does not indicate a higher level of biosimilarity

FDA Meta analysis October 2023

Safety Outcomes When "Switching" Between Biosimilars and Reference Products

- Patients and their health care professionals still have reservations about switching a patient to a biosimilar whose condition is stable on the reference product.

- FDA investigators conducted a systematic review & meta-analysis to determine whether there were safety outcome differences

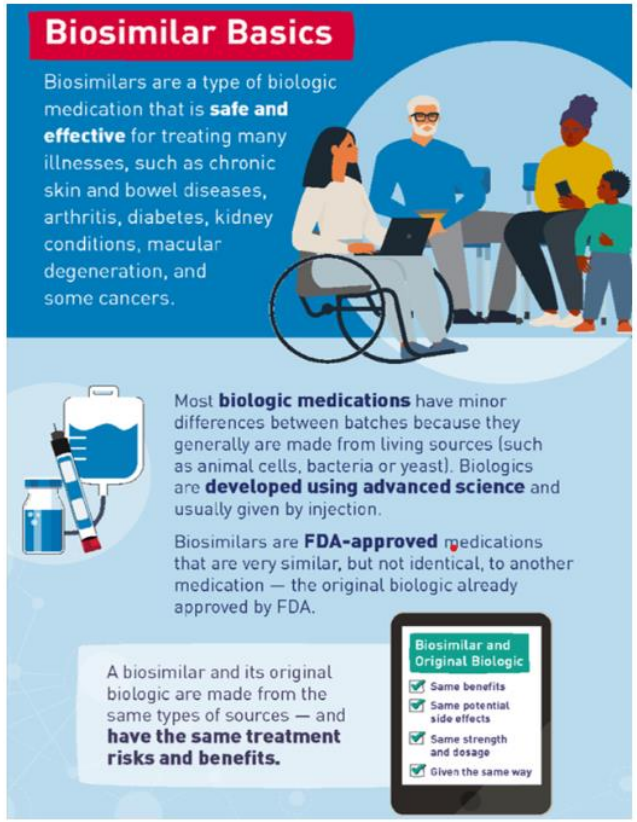
  Patients switched biosimilar & a reference product vs patients no switch

  - Zero difference: Risk of death, SAEs, & treatment discontinuations
  - Immunogenicity: Similar incidences of antidrug antibodies & neutralizing antibodies
  - Immune-related adverse events: anaphylaxis, hypersensitivity reactions, and injections site reactions were similar
  - Based on these data, researchers concluded there were no differences:
    - Risk of death, serious adverse events, or treatment discontinuations between the switch and no-switch arms

- Safety Outcomes When "Switching" Between Biosimilars and Reference Products | FDA

Review: No Safety, Efficacy Issues Found in Patients Who Switched From Originators to Biosimilars (centerforbiosimilars.com)

Ongoing Extensive FDA Educational program:



- Biosimilar Medications as Explained by Identical Twins (PSA) (Duration: 30s)

- **FDA Educational Materials on biosimilars: F**act sheets, videos and infographics for patients and health care professionals and many of them are translated into multiple languages.

First IC Biosimilars W/O switching studies

FDA: Biosimilar and interchangeable landscape ***will continue to evolve***

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- 2015 1st biosimilar was approved, Zarxio (filgrastim-sndz)
- 2019 IC guidance provided a pathway to interchangeability
- 2023 Updated labelling guidance: whether biosimilar or IC biosimiliar
  - NEXSYMEO **is biosimilar to** JUNEXANT
- 2023 FDA meta analysis gave us confidence
  - No difference in risk of death, SAEs, treatment discontinuations and immunogenicity
- First IC designation with no required switching study
  - Insulins: more than 50 years of safety experiences, huge PV data base, simple protein
  - Aflibercept: ocular injection no systemic exposure
  - Denosumab: low risk for immunogenicity
- 2024 Updated IC guidance (FDA intends to revise the Interchangeability Guidance)
    - Experience evaluating analytical differences between biosimilar & reference products their impact on clinical performance.
    - Advancement in technology: Analytical technologies can structurally characterize highly purified therapeutic proteins and model in vivo functional effects with a high degree of specificity and sensitivity using in vitro biological and biochemical assays.
    - Applicants may provide an assessment of why the comparative analytical and clinical data provided in the application or supplement support a showing that the switching standard set forth in section 351(k)(4)(B) of the PHS Act has been met.
- 2025 IC Device guidance: An important next step for IC development

Thank you.