IMS Health & Quintiles are now IQVIA™

Methodologic Considerations for Non-Interventional Studies Evaluating Outcomes of Originator-to-Biosimilar Switching

Setting the Stage

Jaclyn L. F. Bosco, PhD, MPH

August 24, 2018

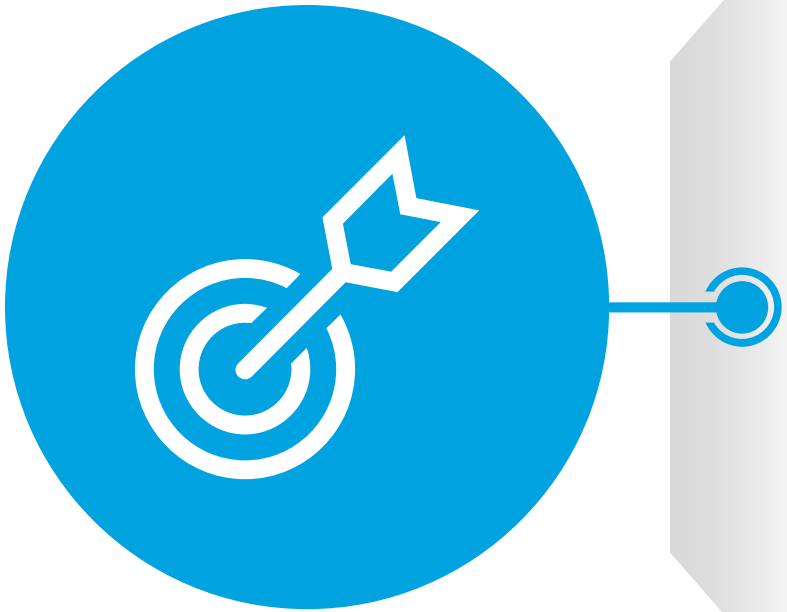
ICPE Prague

Disclosures

- I am a full-time employee of IQVIA and perform no research or consultancy outside of that employment.
- I am a Scientific Advisor for the BBCIC Switching and Comparative Effectiveness Working Groups
- I accept no personal consulting fees.
- I have participated in the design and conduct of studies of the safety and effectiveness and use of biologics and have designed research for the purpose of studying biosimilars. None of my research activities are described here.
- No confidential or proprietary data are included in these slides.

Symposium Objective

Within the anti-TNF scenario

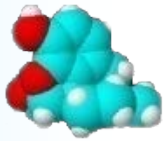


To provide an overview of the challenges in designing and conducting non-interventional studies of biosimilar switching patterns and outcomes and to offer methodological recommendations to mitigate these challenges, specifically regarding study design, variable measurements, bias, and analytic approaches

The Big Picture

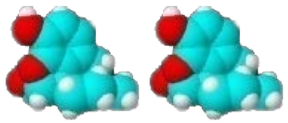
CHEMICALLY SYNTHESIZED

Small molecule



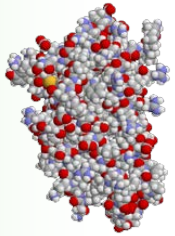
- Proof of quality and bioequivalence
- No substantial clinical data required
- Reference to originator's data

Generics



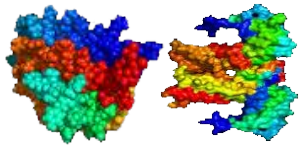
MADE FROM LIVING TISSUE

Biological medicine



- Different manufacturing processes can yield differences in end product
- After the quality of a biological medicine is demonstrated, some non-clinical and clinical studies are currently required
- Immunogenic response not consistently predicted so testing is required

Biosimilars



Adapted from Goel N et al. Operational Challenges Associated with biosimilar drug development. J Clinical Studies. 2015;7(2):20-17
http://issuu.com/mark123/docs/jcs_-_volume_7_-_issue_2_909325a2730cb9

Terminology

Term	Definition
Biosimilar[1] 	• Biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components • No clinically meaningful differences between the biological product and reference product in terms of the safety, purity and potency
Interchangeability[2]	• Medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient on the initiative or with the agreement of the prescriber
Switching[2]	• Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment
Substitution[2]	• Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber

1. Section 351(k) of the Biologics Price Competition and Innovation Act of 2009
2. Ebbers HC, Chamberlain P. GaBI, 3(2):88-93; 2014

FDA has approved 12 biosimilars for 8 originators (July 2018)[1]

Non-proprietary name	Biosimilar Brand	Developing company	Approved
Filgrastim-sndz	Zarxio®	Sandoz	Mar-15
Filgrastim-aafi	Nivestym™	Hospira/Pfizer	Jul-18
Infliximab-dyyb	Inflectra™	Celltrion	Apr-16
Infliximab-abda	Renflexis®	Samsung Bioepis	Apr-17
Infliximab-qbtx	Ixifi®	Pfizer Inc	Dec-17
Etanercept-szzs	Erelzi™	Sandoz	Aug-16
Adalimumab-atto	Amjevita™	Amgen	Sept-16
Adalimumab-adbm	Cyltezo®	Boehringer Ingelheim	Aug-17
Pegfilgrastim-jmdb	Fulphilia™	Mylab GmbH	Jun-17
Bevacizumab-awwb	Mvasi™	Amgen Inc	Sep-17
Trastuzumab-dkst	Ogivri™	Mylan GmbH	Dec-17
Epoetin alfa-epbx	Retacrit®	Hospira/Pfizer	May-18

Note: To date, none of the approved biosimilars in the U.S. have been approved as an interchangeable product

1. https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm580432.htm

Interchangeability and Substitution

UNITED STATES

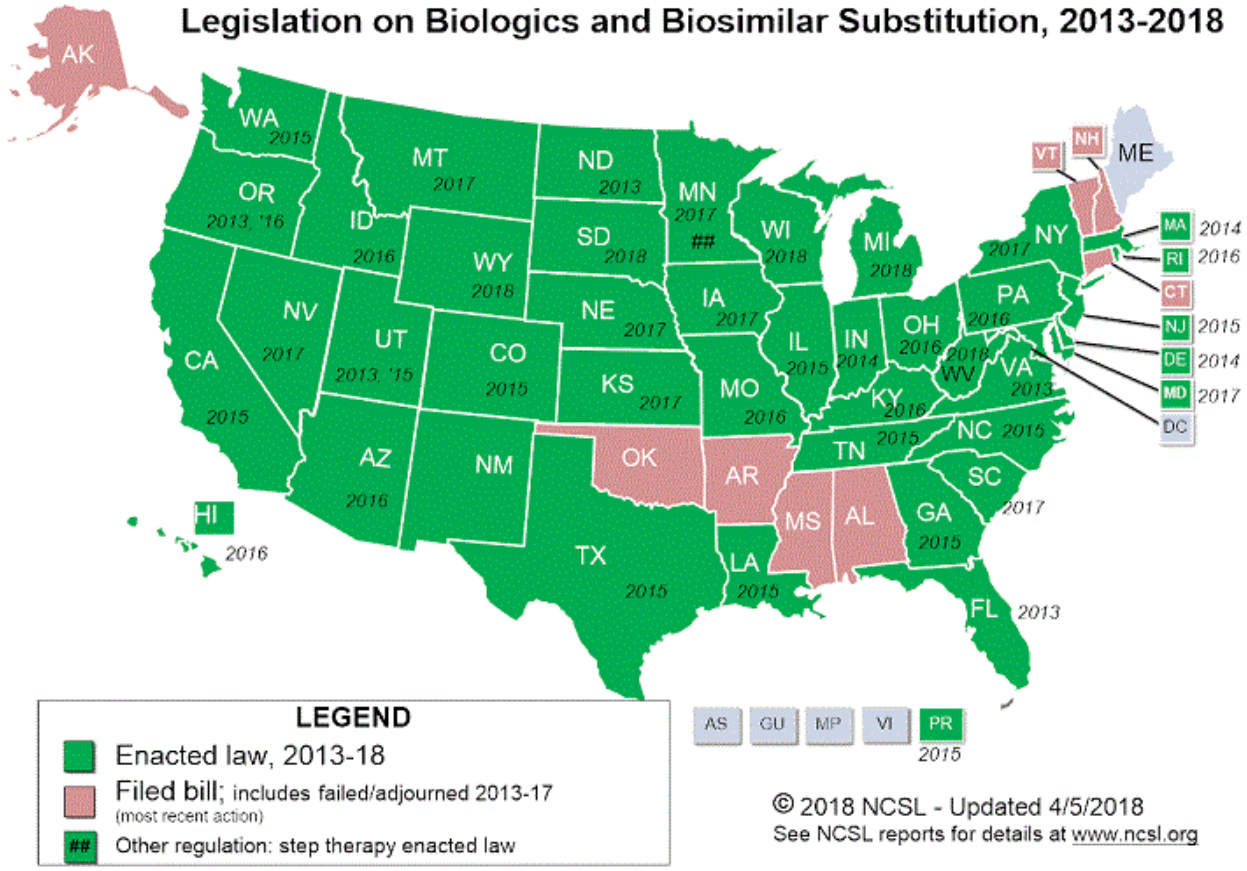
- Defined in Biologics Price Competition and Innovation Act (2009)
- FDA can approve a product as interchangeable
- Individual states control the act of pharmacy-level substitution
- FDA issued draft guidance in January 2017
- 45 US States and Puerto Rico have passed legislation addressing biosimilar substitution
- None of the approved biosimilars have been granted interchangeability status yet

Adapted from GaBI Journal Editor, 2017

Substitution Legislation in the U.S.

FDA approval of interchangeable status must be granted

- State legislation varies with regard to:
  - Timeframe for prescriber/doctor communication or notification and if recoded in EHR
  - Patient notification and/or consent
  - Prescriber has ability to block substitution by indicating “Brand Medically Necessary”
  - Whether pharmacy records need to be retained and for what duration
  - If a list must be posted for interchangeables

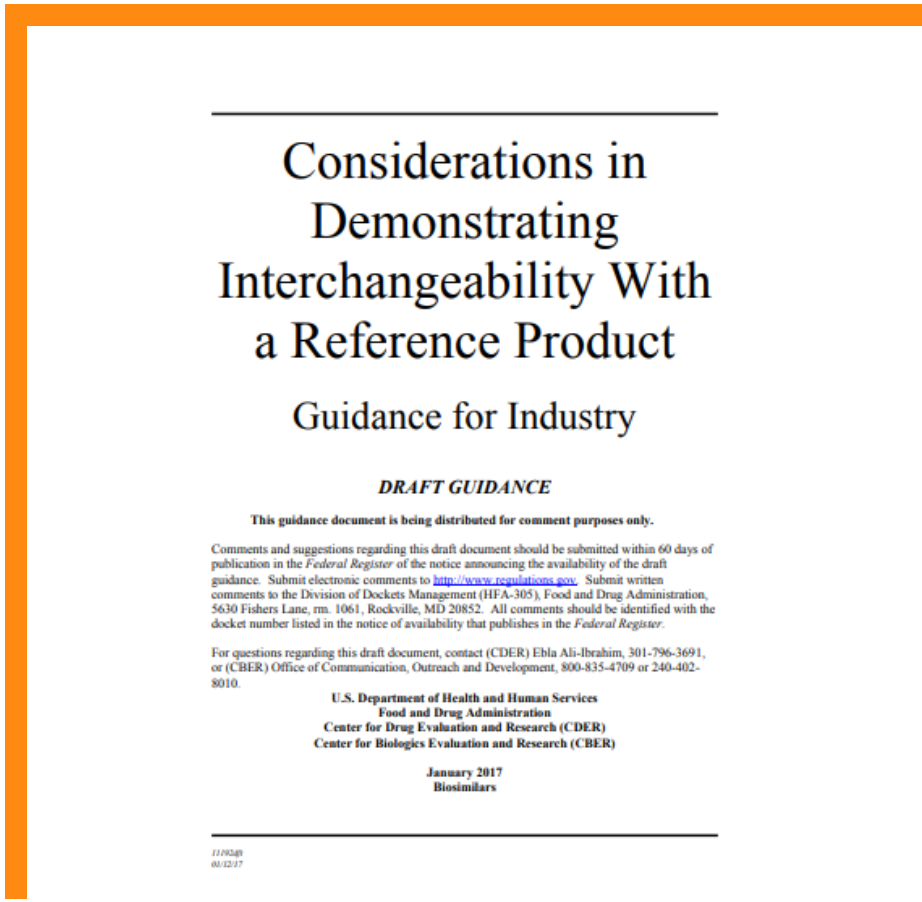


http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars.aspx

Demonstrating Interchangeability

Per FDA Draft Guidance

- Generally requires prospective, **controlled switching studies** of human patients showing the **same clinical result between** the biosimilar and the reference biologic
- **No greater risk with alternating or switching** between use of the biosimilar and the reference biologic **compared to maintaining** the patient on the reference product for a biological biologic that is administered more than once
- Data from **post-marketing non-interventional studies** may be helpful when considering **necessary data** to support demonstration of interchangeability
- **Post-marketing surveillance data** may **complement** data from **pre-approval switching studies** to **address residual uncertainty** in demonstrating interchangeability



Considerations in Demonstrating Interchangeability With a Reference Product

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Ebla Ali-Ibrahim, 301-796-3691, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

January 2017
Biosimilars

1119Dft
01/12/17

https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf

Access and Distribution for Biologics

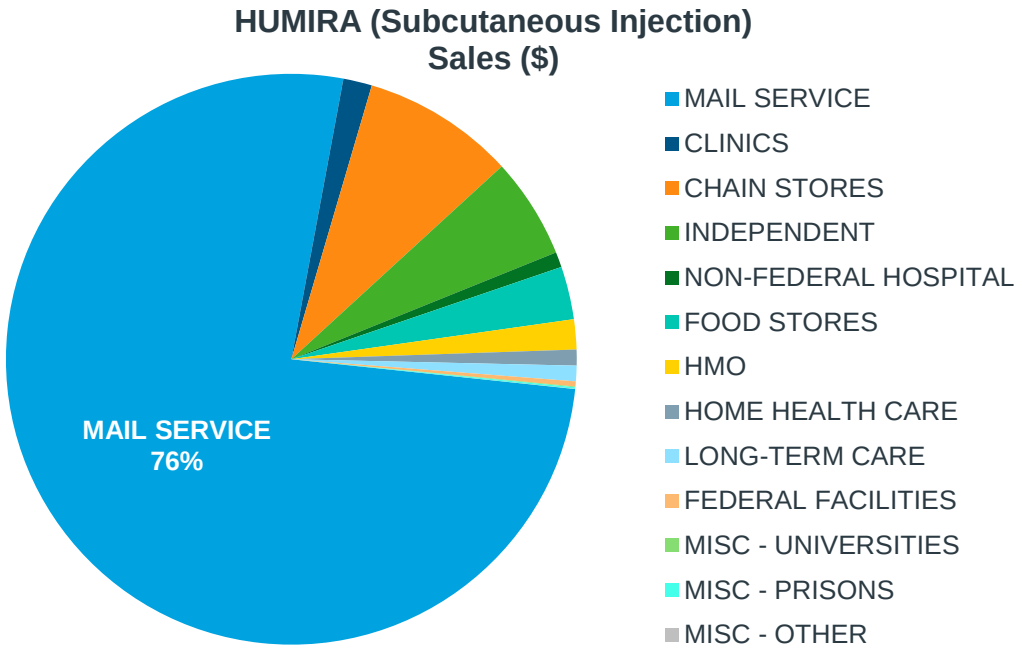
Think about what the biologic is being used for and how it is supplied

- Self-injected and orals distributed through retail pharmacies
- Specialty pharmacy distribution can be used to track infusion products
  - In US, administered in doctors' offices and outpatient hospital settings
  - In EU, almost always, in outpatient hospital settings

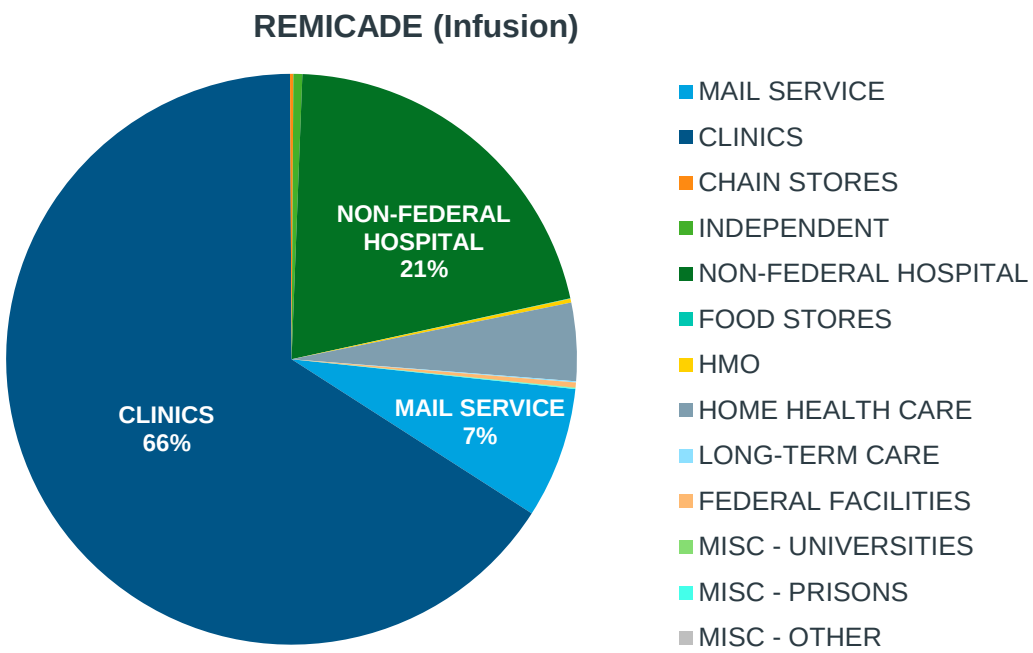
Where do you find prescription information?

Depends on how the product is administered

- Majority of **prescription-based product** sales for **biologics** go through **specialty pharmacy distribution**

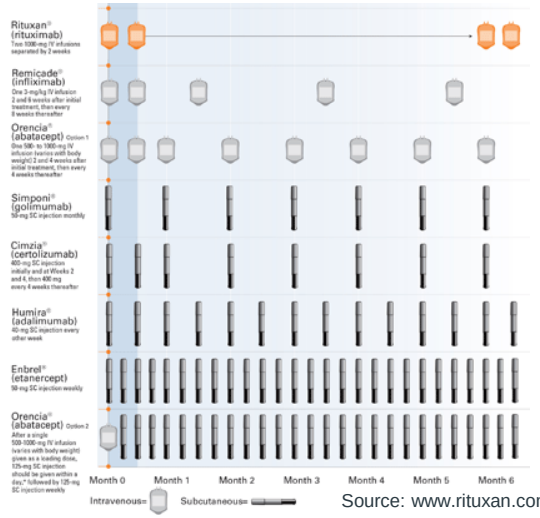


- A large proportion of **infused products**, such as Remicade are dispensed in the **outpatient hospital setting**



Source: National Sales Perspective (NSP)

Dosing schedules and administration modes vary across products making consistent measurement challenging



Source: www.rituxan.com

- While subcutaneous products have consistent days' supply reported in the data, infused products' data **does not**
- Accurately tracking dosing is much more complicated, especially in the hospital data where dosing information is less consistently entered
- Each of the products has a **different dosing schedule** and time period that it covers
- Several products have **loading doses** that begin their course of treatment. When translating scripts to dollars, or patients, or when estimating compliance, this needs to be considered

Source: www.stelarainfo.com

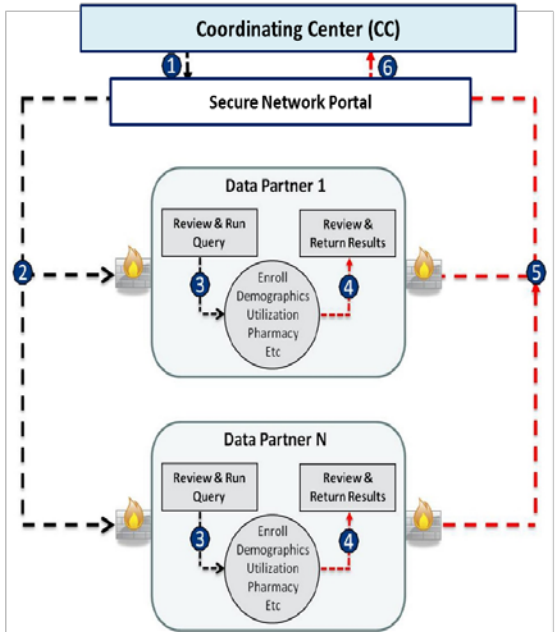
BBCIC Surveillance –Leveraging Sentinel Capabilities

The AMCP BBCIC strategy provides a unique opportunity for Managed Care to support public knowledge of biologic and biosimilar drugs with robust science.

BBCIC leverages the Sentinel Initiative → Improves the efficiency and cost-effectiveness of post-marketed observational studies.

BBCIC actively monitors biosimilars and innovators → Anonymous data from ~150 million patients

BBCIC is a multi-stakeholder collaboration → Diverse expertise allows for a larger voice with more credibility



1- CC submits query on behalf of work group (a computer program)

2- Data Partners retrieve query

3- Data Partners review and run query against their local data

4- Data Partners review results

5- Data Partners return results to CC via secure network

6- Results aggregated by CC and sent to work group

A forum for collaboration between managed care organizations, integrated delivery networks, PBMs, pharma companies and research institutions

Contact Information

Jaclyn Bosco, PhD, MPH
Senior Director,
Global Scientific Head, Epidemiology and Outcomes Research
Real-World Evidence Solutions

Jaclyn.Bosco@iqvia.com
+1 (617) 674-8460