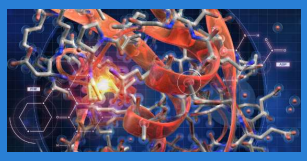
Biosimilars - Innovative Molecules Responding to the Demand for Biologics Treatment



Marile L. Santamarina MS, PharmD, CPh, CDCES, CPT
Innovative Pharmacy Practice Conference
September 9-10, 2023

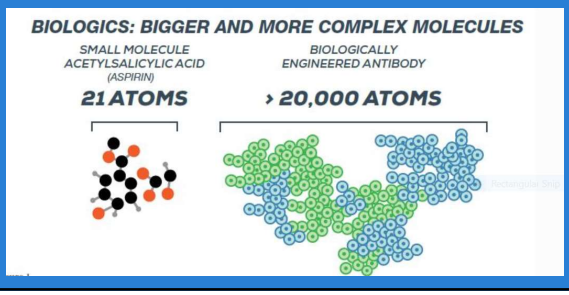
1

Objectives

1) Describe development of biosimilars
1) Discuss common misconceptions with biosimilars.
2) Describe nocebo effects with Biosimilars.
3) Identify role of the pharmacist in the adoption of Biosimilars.

2

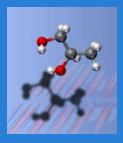
Next-generation medicine innovation are Biologics

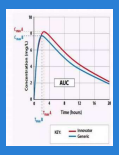


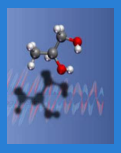
3

Small Molecule / Conventional Drugs

- "Conventional" or small molecule drug
  - Identical molecules synthesized chemically in the laboratory
  - Smaller molecules
  - Less targeted effect → may result in → untargeted effects → more side effects and possible toxicity
  - Easier administration → oral dose





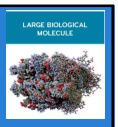


Brand name

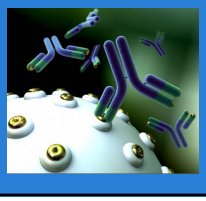
Generic

4

Large Molecule / Biologic Drugs



- Biologic products
  - Large molecules ranging in size ~ 3,000 – 150,000 Da (usually having > 1,300 amino acids)
  - Protein → therapeutic effect → monoclonal antibodies, gene therapy
  - Binding capacity is highly specific → targeted molecules → modulate immune system
  - Biosimilars are synthesized in living organisms → Cell lines
  - Biosimilar are mostly injectable products



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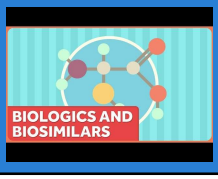
Rationale for Developing Biosimilars

- Rationale for Biosimilars developed in US
  - Biologics USE accounted ~2% of drug use
  - Biologic EXPENDITURE accounted for ~37% of drug use
- In 2010 → as part of the Affordable Care Act → Biologics Price Competition Act (BCPIA)
  - Provided an "Abbreviated Pathway" for Biosimilar drug approval
- Biosimilars in Europe
  - In 2006 → Europe approved their first biosimilar → Somatotropin
  - In 2022 – cumulative cost savings resulting the impact of competition of biosimilars reached more than € 30 billion
  - Europe has 93 biosimilars as of May 2023

6

Development of Biologics

- A biosimilars can be marketed once the period of exclusivity of the biologic reference product has expired
- Period of exclusivity of biologics ranges between 8-12 years
- The biosimilar drug demonstrates to FDA → There is NO CLINICALLYT MEANINFUL DIFFERENCE the efficacy, safety or immunogenicity between the reference product and the biosimilar



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HEALTH INC.

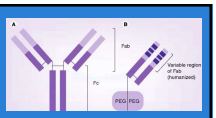
AbbVie's blockbuster drug Humira finally loses its 20-year, $200 billion monopoly

January 31, 2023 · 6:00 AM ET

By Leslie Walker, Dan Gorenstein

8

Rationale for Developing Biosimilars

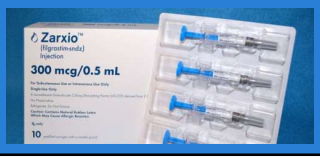


- Increase medication innovation
- Increase competition between pharmaceutical companies → Reduce drug prices
  - Humira cost without insurance → $6,922 / month
- Increase patient access to medications
  - The report finds the average sales price of biosimilars → 50% less than the biologic originator
  - Competition from biosimilars has reduced the average sales price of originator product by ~25%
  - The market for biosimilar continues to expand and competition among biosimilars has reduced the average sales price or their originator product by an average of 25%

9

Biosimilars approvals in the US

- Biologics Price and Competition Act → abbreviated pathway for biosimilars
  - No dosing finding studies are needed → determined by the reference product
  - Clinical trials conducted are smaller and shorter
  - No need to conduct clinical trials for "every indication" seeking FDA approval → EXTRAPOLATION
- First biosimilar approved in the US Zarxio (filgrastim-sndz) -- 2015
- There are 41 Biosimilars FDA



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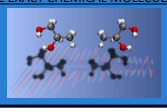
Generic Drugs

PRODUCE EXACT CHEMICAL MOLECULAR COPIES



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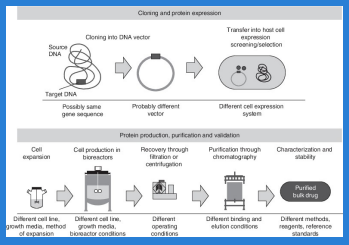
Biosimilars



PRODUCED IN LIVING ORGANISMS (CELL LINES) grown in vitro and
PRODUCE SIMILAR MOLECULAR ENTITIES

12

In Nature … No two oaks are identical

They are similar !!!

13

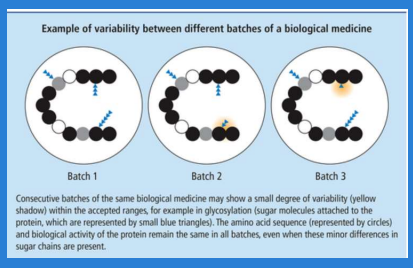
Originator Drug / Biosimilar Drug

Originator Biologic

Biosimilar

14

Biosimilars are ALL Biosimilars of themselves



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Manufacturing changes of Originator product and Biosimilar

Characteristics of originators and corresponding biosimilars of TNF-α-i products approved in the EU up to May 2020.

Active substance	Trade name	Company code (BS order)	EU MA date (mm-yyyy)	Number of post-approval MCs(n)	Follow-up to May 2021 (years)	Average incidence rate of MCs/year (high-risk/year)
Infliximab	Remicade®	Originator (RP)	08-1999	112	21.8	5.2 (0.8)
	Remsima® Inflectra®	CTP13(BS1)[b]	09-2013	133	7.7	17.3 (2.7)
	Flixabi®	SB2 (BS2)	05-2016	57	5.0	11.4 (1.4)
	Zessly®	GP111 (BS3)	05-2018	9	3.0	3.0 (0.0)
Etanercept	Enbrel®	Originator (RP)	02-2000	175	21.3	8.2 (0.9)
	Benepali®	SB4 (BS1)	01-2016	43	5.3	8.1 (0.5)
	Erelzi®	GP2015 (BS2)	06-2017	30	3.9	7.7 (0.0)
	Nepexto®	YLB113 (BS3)	05-2020	8	1.0	8.0 (0.0)
Adalimumab	Humira®	Originator (RP)	09-2003	124	17.7	7.1 (1.0)
	Amgevita® Solymbic®[a]	ABP501 (BS1)[b]	03-2017	11	4.2	2.6 (0.2)
	Imraldi®	SB5 (BS2)	08-2017	45	3.8	12.0 (0.5)
	Cyltezo®[a]	BI695501 (BS3)	11-2017	1	1.3[c]	0.8 (0.0)
	Hefiya® Halimatoz® Hyrimoz®	GP2017 (BS4)[b]	07-2018	28	2.8	9.9 (0.7)
	Hulio®	FKB327 (BS5)	09-2018	18	2.7	6.8 (0.7)
	Idacio® Kromeya®	MSB11022 (BS6)[b]	04-2019	7	2.1	3.4 (0.0)
	Amsparity®	PF06410293 (BS7)	02-2020	0	1.3	-

Lasamil AM, Giezen TJ, Egberts TC et al. nature and timing of post-approval manufacturing changes of tumour necrosis factor α inhibitor product: A 20-yearfollow-up study of originators and biosimilars. Eur J Pharmaceu Sci 175 (2022) 106227

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Development of Biosimilars

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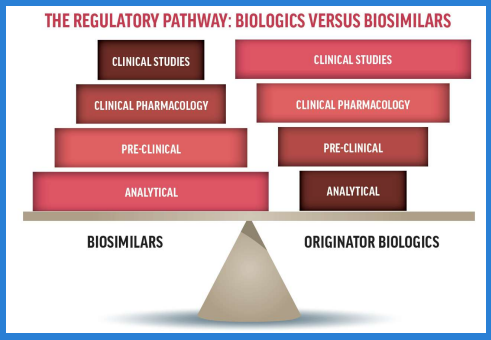

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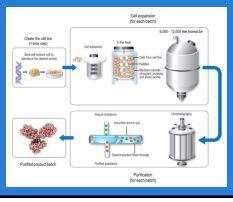
Biosimilar FDA Approval Process

- Is a rigorous approval process which include:
  - Biosimilar protein molecules production and purification
  - Physicochemical and Functional assessment of the molecular entity → Longest period
  - Pharmacokinetic / Pharmacodynamic studies
  - Clinical Trials → Smaller and shorter studies
  - Approval process ~ 7- 8 yrs



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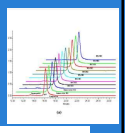
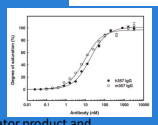
Biosimilars FDA Approval Physicochemical and Functional Assessment



- Assessment of critical quality attributes of molecular entity
  - Longest period of the biosimilar development program → up to 5 yrs
  - Peptide mapping - Primary structure of molecule
  - Purity of biosimilar
  - Biological functioning and potency compared to originator

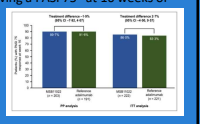


- Pharmacokinetic parameters → Cmax and AUC
- Randomized Clinical Trials → smaller (# patients), fewer (# trials)
  - Efficacy, Safety and IMMUNOGENICITY
- Biologics must demonstrate that the molecule is HIGHLY SIMILAR to the originator product and exhibits NO CLINICALLY MEANINFUL differences with respect to efficacy, safety and immunogenicity when compared to originator product

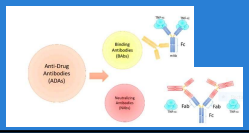
20

FDA Approval of Biologics and Biosimilars

- Efficacy → Primary Endpoint – Plaque Psoriasis study using % patients achieving a PASI 75" at 16 weeks of treatment with reference product and the biosimilar



- Safety → Adverse Emergent Adverse Events is similar between the reference product and the biosimilar
- Immunogenicity → the incidence of "Antidrug Antibodies" and "Neutralizing Antibodies" is similar in the biosimilar and the reference product



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Question #1

During the FDA approval process of a biosimilar. The biosimilar must demonstrate that the molecule structure, PK parameters, safety, efficacy and immunogenicity of the biosimilar is highly similar and will have no clinically meaningful differences with respect to efficacy, safety and immunogenicity when compared to the reference product.

a) True

b) False

22

Biologics and Biosimilar Nomenclature

Core name /non-proprietary name – 4-lower case characters
Example Idacio® (adalimumab-aacf)

Since 2019 – FDA required that all biologics approved (originator or biosimilar) will require a 4-letter suffix.

- Distinguish identifier for pharmacovigilance
- Distinguish identifier for insurance coverage
- Distinguish identified for dispensing
- Distinguish identifier for patients and provider

23

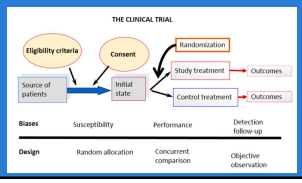
Misconceptions associated with Biosimilars

24

Biosimilars and Extrapolation

- Biosimilar do not conduct clinical trials for EVERY SINGLE indication requested from the FDA

- By FDA using the concept of Extrapolation
  - Data provided in the Biosimilar application
  - Reference product safety, efficacy and immunogenicity data presented to FDA
  - Indication pathophysiology



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Interchangeability of Biosimilars

- Only use US → Definition Interchangeability = a interchangeable biosimilar may be substitute at the time of dispensing by a pharmacists without the intervention of the prescriber this varies depending on every State Board of Pharmacy

- Interchangeable designation does not exist in Europe → when the biosimilars demonstrate no clinically meaningful difference in terms efficacy, safety and immunogenicity between reference product and biosimilar → all biosimilar are interchangeable in EU

- EMA (first biosimilar approved-2006). In 2022 – analyzed biosimilar data concluded → there is no evidence that switching between a biosimilar and its reference product will increase the risk of immunogenicity

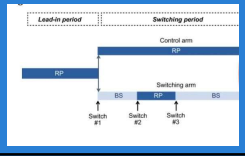
26

Interchangeability of Biosimilars

- The FDA has created a new regulatory designation → Interchangeability

- Biosimilars requesting "Interchangeable" designation must provide to the FDA one study having at least 3 switches between reference product and biosimilar

- Biosimilars having the interchangeability designation are not more similar or superior to biosimilars not having such designation



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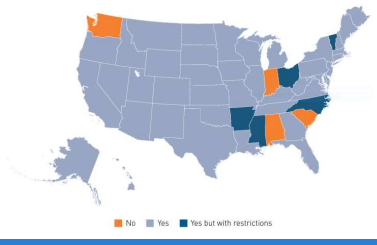
Can a pharmacist substitute an interchangeable without prior prescriber approval?



Florida board of Pharmacy s. 262. (2) A pharmacist may only dispense a substitute biological product for the prescribed biological product if: (a) The United States Food and Drug Administration has determined that the substitute biological product is biosimilar to and interchangeable for the prescribed biological product

Evans Cans Gibofsky A. Biosimilars for Immune-mediated Inflammatory Diseases- A Managed Care Perspective. AJMC 2022;S234-S239

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Two Pager — MIKE LEE US SENATOR for UTAH — June 20, 2023

Biosimilar Red Tape Elimination Act

- Introduction of "Interchangeability" by the FDA has created a two-tiered system for biosimilars approval which has confused → physicians, patients and State Board of Pharmacy about the safety and efficacy of biosimilars
- This two-tiered system has affected the adoption of biosimilars in the US
- Some State Board of Pharmacy have passed laws "not allowing" pharmacists from automatically substituting a reference biologic for its biosimilar unless they have the interchangeable designation from the FDA
- As of May 2023 →FDA has approved 41 biosimilars - 4 biosimilars have applied for interchangeability designation

https://www.lee.senate.gov/2023/7/lee-seeks-increased-competition-in-biological-drug-market

29

Question #2

As part of the approval process of a biosimilar; the biosimilar must conduct clinical trials in each one of the indications that the biosimilar is seeking approval for

a) True

b) False

30

Question #3

A biosimilar having “interchangeable” designation has demonstrated greater efficacy, safety and immunogenicity than a biosimilars not having “interchangeable” designation

a) True

b) False

31

Question #4

Interchangeability is regulatory designation independent of the approval process as a biosimilar

a) True

b) False

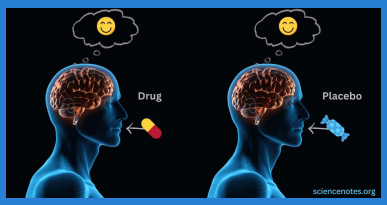
32

Biosimilar and the Nocebo Effect

33

Placebo

- A drug product without an active pharmaceutical ingredient which may cause a physiological response on a patient based on the patient's psychological state
- The average placebo response rate in clinical trials is ~ 34%



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Nocebo Effect

- The worsening of symptoms or onset of new clinical issues resulting from a patient's negative belief towards a drug product despite receiving an a pharmaceutically active drug product
- Nocebo effect has been observed in some patients switching from a high-cost biologic to a new lower-cost biosimilar – claiming loss of efficacy with the biosimilar
- A review of randomized blinded clinical trials and their open-label extension period where patients were transition from reference product to the biosimilar discontinuation rates were higher in the open-label studies (14.3%) versus in the blinded clinical trials (6.9%)

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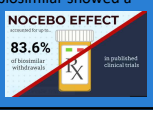
Nocebo Effect

- Very difficult to assess if lack of therapeutic efficacy from a reference product to biosimilar
- Could it be that a given biosimilar does not work for a particular patient?
- Is the lack of efficacy to switch from reference product to a biosimilar the result of "Nocebo Effect"?
- A review of multiple clinical trials in patients diagnosed with rheumatoid and psoriatic arthritis after patients were switched from reference product to biosimilar showed a discontinuation therapy rate of 83.6%



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Question # 4

The use of biosimilars has been associated with patients experiencing “Nocebo effect”.

a) True

b) False

37

Role of the Pharmacist in the adoption of Biosimilars

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Pharmacist and Biosimilars adoption

- Provide → EDUCATION, EDUCATION, EDUCATION … patients and providers
- Biologics/ biosimilars treat chronic debilitating disease – oncology, irritable bowel disease (peds & adults), rheumatic conditions (peds & adults), plaque psoriasis (peds & adults), ankylosing spondylitis
- Patients do not understand the difference between biologics and biosimilar
  - FDA approval process
  - Two-tiered designation → interchangeable or not interchangeable

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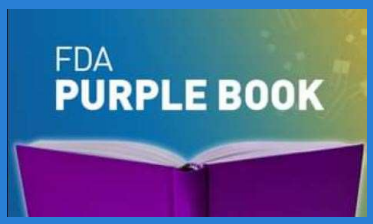
Pharmacists and Adoption of Biosimilars

- Patients who have achieve remission of their disease →DO NOT want to switch to a biosimilar → Ask the patient why?
- HCP patients that have patients that have achieved remission on a reference product are reluctant to switch to a biosimilar
- Insurance coverage will cover biosimilar rather than reference product

40

Biosimilars FDA resource



https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/purple-book

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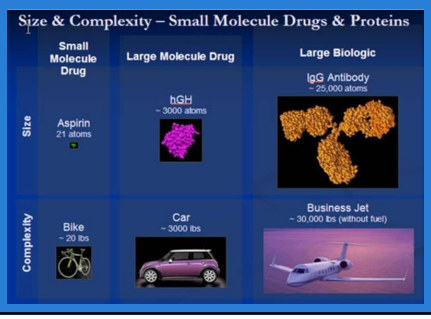
Prescription Drugs Categories



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Thank you for your kind attention !!!

43

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15) Gasteiger C, Gasteiger N, Petrie KJ. Pharmacists' confidence in explaining biosimilars to patients before a nationwide medicine change: a cross-sectional study. *Explor Res Clin Soc Pharm.* 2022;8:100199.

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