How Similar is a Biosimilar?

Sophia Zhang Humphreys, Pharm.D., MHA
Director, Pharmacy Clinical Services
Providence St. Joseph Health
Seattle, Washington

1

Learning Objectives

- Describe the difference between biologic medications and small molecule chemical medications.
- Explain the definitions of reference product, biosimilar product, and an interchangeable product; and understand the differences between them.
- Compare and contrast biosimilar products and generic products.
- Summarize the abbreviated approval pathway for biosimilar and interchangeable products.

2

Agenda

- Review definition of biologic products
- Financial impact of biologic medications
- Can generic products be made for biologic medications?
- Biologics Price Competition and Innovation Act: Biosimilar approval pathway
- Biosimilar and interchangeable products
- Summary and post test

3

What Is a Biologic Medication

- According to FDA biologic products are:
  - Produced from **living organisms**, such as plant and animal cells or microorganisms
  - Large and complex molecules
  - Used to diagnose, prevent, treat and cure medical conditions and diseases
  - Regulated by the FDA
  - The innovative compound is called the **reference product**

4

History of Biologic Medications

- Insulin (Humulin) was the first commercially available biologic medication
- Insulin was initially discovered in the early 1920's
  - A Nobel Prize was awarded to Banting, Best, and Macleod in 1923, for the discovery and isolation of insulin
  - In 1982, Humulin was marketed in the U.S. as the first insulin product manufactured via **recombinant DNA** technology

5

Financial Impact of Biologic Drugs

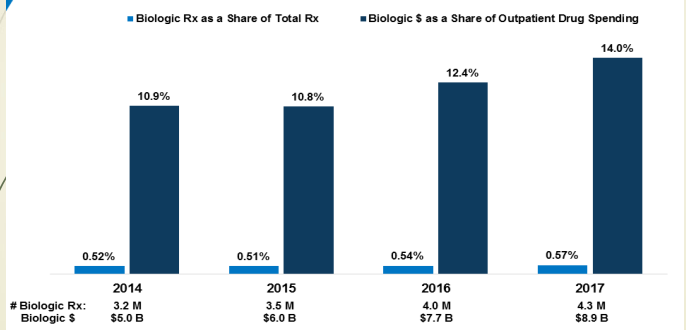
- Biologic medications are much **more expensive** than small molecule chemical drugs
- A high percentage of the drug cost increases in the **past five years** are due to biologic drugs
- More and more new biologics are coming
- The newest biologic medication has a price tag of $2.125 million per treatment

6

Biologic Medication Spending

Figure 10

Biologics as a Share of Number of Medicaid Prescriptions and Medicaid Outpatient Drug Spending, 2014-2017



Note: Spending amounts do not include rebates.
Sources: Kaiser Family Foundation Analysis of 2014-2017 State Drug Utilization Data; Biologics Purple Book as of April 2018; Wolters Kluwer Clinical Drug Information, Inc., 2018.

KFF

7

Questions

- What are the differences between **biologic** medications and **chemical** medications?
- When was the first biologic medication marketed in the US?

8

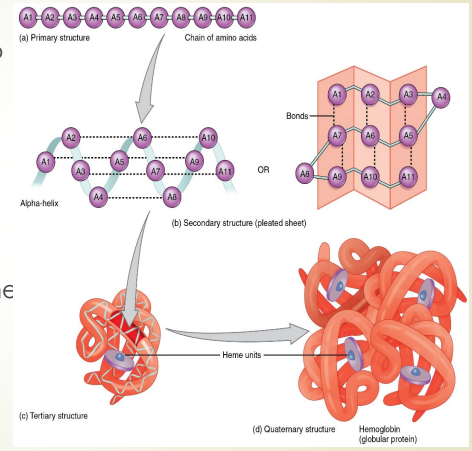
Historically, Generic Products Have Provided Lower Cost Alternatives

- Quick review of Drug Price Competition and Patent Restoration Act (1984), the Hatch-Waxman Act.
  - Outlines the process for pharmaceutical manufacturers to file an Abbreviated New Drug Application (ANDA) for approval of a generic drug by the FDA
  - Applies only to **small molecule** chemical medicines
  - Requires generic products to be **identical** to their brand name counterparts

9

Biologic Medication Molecular Structures

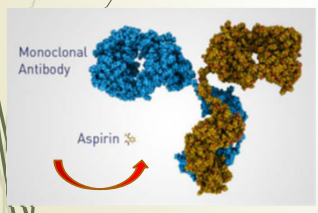
- Long and complicated amino acid sequences forms the primary structure
- Folding structures
  - Secondary intra-molecule hydrogen bond
  - Tertiary separation of the hydrophilic and hydrophobic portions of the molecule
  - Quaternary folding
- Glycosylation



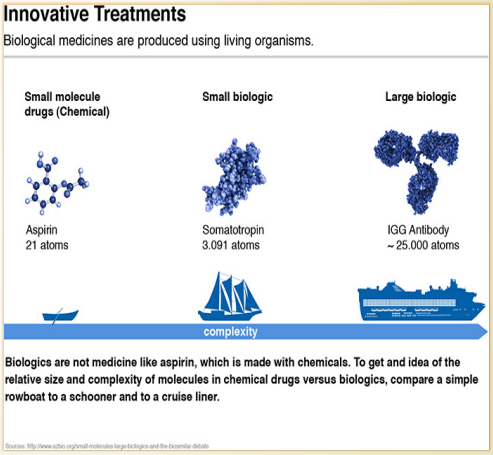
10

Impossible To Make Generics For Biologics

- Large molecule size
- Complex structure
- Impossible to duplicate
- Developed in living organisms



Source: biological product definitions, Food & Drug Administration.



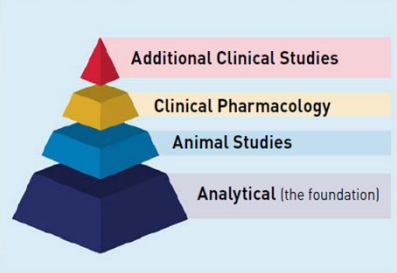
11

Biologics Price Competition & Innovation Act

- BPCIA is a subsection of the Patient Protection and Affordable Care Act (2010)
- It establishes "a biosimilars pathway, balancing innovation and consumer interests."
  - Abbreviated process for manufactures to gain FDA approval for products highly similar to the reference compounds without meaningful clinical differences
  - Biosimilars are not generics, thus not identical to innovator products

12

Biosimilar Approval Pathway



Adopted from: Biosimilar Product Regulatory Review and approval. US. FDA. 2019

1. Extensively analyze the structure and function
2. Animal model studies (toxicity studies)
3. Pharmacodynamic and pharmacokinetic studies
4. Clinical trials if FDA consider it necessary

13

Highly Similar To Reference Compound

Biosimilar products are HIGHLY SIMILAR to reference compounds in:

- Safety and purity
- Efficacy and potency
- Pharmacokinetics
- Pharmacodynamics
- Immunogenicity

There are no clinically meaningful differences

Source: https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars

14

Differences Between Generics & Biosimilars

	Biosimilars	Generics
Molecular Structure	Big & complex molecules	Small & simple molecules
Manufacturing process	From living system, very complicated	Chemical synthesis, relatively simple
Compare to Innovator/ Reference drug	Highly similar, but not identical	Identical to innovators

15

Questions

- Can generic products be made for biologic medications?
- Do all biosimilars need extensive clinical trials?

16

FDA Approved Biosimilars

Biosimilars	Reference Compounds
adalimumab	**Humira**
adalimumab-atto (Amjevita)	
adalimumab-adbm (Cyltezo)	
adalimumab-adaz (Hyrimoz)	
bevacizumab	**Avastin**
bevacizumab-awwb (Mvasi)	
Bevacizumab-bvzr (Zirabev)	
epoetin alfa	**Epogen**
epoetin alfa	**Procrit**
epoetin alfa-epbx (Retacrit)	
etanercept	**Enbrel**
etanercept-szzs (Erelzi)	
etanercept-ykro (Eticovo)	
filgrastim	**Neupogen**
	Granix (tbo-filgrastim)
filgrastim-sndz (Zarxio)	
filgrastim-aafi (Nivestym)	

17

FDA Approved Biosimilars (cont'd)

Biosimilars	Reference Compounds
infliximab	**Remicade**
infliximab-dyyb (Inflectra)	
infliximab-abda (Renflexis)	
infliximab-qbtx (Ixifi)	
pegfilgrastim	**Neulasta**
pegfilgrastim-jmdb (Fulphila)	
Pegfilgrastim-cbqv (Udenyca)	
rituximab	**Rituxan**
rituximab-abbs (Truxima)	
rituximab-pvvr (Ruxience)	
trastuzumab	**Herceptin**
trastuzumab-dkst (Ogivri)	
trastuzumab-pkrb (Herzuma)	
Trastuzumab-dttb (Ontruzant)	
Trastuzumab-qyyp (Trazimera)	
Trastuzumab-anns (Kanjinti)	

18

Interchangeable Biosimilars

- An interchangeable product must:
  - Be **Biosimilar** to the reference compound
  - Produce the **same clinical outcome** in all patients, all indications
  - Present **no increased risk** or **reduced efficacy** if the products are switched back and forth with the reference compound.

19

To Substitute or Not To Substitute?

- A pharmacist **may *not*** substitute a Biosimilar for its reference product
- **Interchangeable** biosimilars may be substituted by a pharmacist without the authorization of the provider who ordered the reference compound
- **State laws vary**, please check with your local BOP

20

Questions

- Can one manufacture a generic product for a biologic medication?
- Are all biosimilar products interchangeable with their reference compounds?

21

References

- 1. Rosenfeld L. Insulin: discovery and controversy. Clin Chem. 2002;48:2270–88.
- 2. Medicine Use and Spending in the U.S. A Review of 2017 and Outlook to 2022
  IQVIA Institute for Human Science Report, April 19, 2018.
- 3. Roy, A. Biologic Medicines: The Biggest Driver Of Rising Drug Prices. Forbes, The Apothecary. March 8, 2019.
- 4. Gottlieb S. Biosimilars: policy, clinical, and regulatory considerations. Am J Health Syst Pharm. 2008;65(suppl 6):S2-S8.
- 5. FDA. Guidance for Industry. Scientific considerations in demonstrating biosimilarity to a reference product. Accessed January 24, 2013.
- 6. Cauchi, R. State Laws and Legislation Related to Biologic Medications and Substitution of Biosimilars. October, 2018.
- 7. Graph source:
  - http://www.azbio.org/small-molecues-large-biologics-and-the-biosimilars-debate
  - https://study.com/academy/lesson/proteins-structure-function-types.html

22

Contact Information

Sophia Zhang Humphreys, Pharm.D., MHA
Director, Pharmacy Clinical Services
Providence St. Joseph Health

1801 Lind Ave SW, Renton, WA 98057
Office Phone: 425-525-3711

Email: Sophia.Humphreys@providence.org
Sophiazhumphreys@gmail.com

23