Biosimilars: Is the Future Safer, More Cost-Effective, and Efficacious?

Daniel Wojenski, PharmD, BCPS, BCOP
Hematology/Oncology Practice Coordinator
PGY2 Hematology/Oncology Residency Coordinator
Northwestern Memorial Hospital

Disclosures

- Daniel Wojenski has disclosed that he is on the speaker's bureau for Sanofi Oncology

All conflicts resolved through peer review

Objectives

- Define biosimilars and explain the difference between biologics and generic drugs
- Review the regulatory process for biosimilars by the FDA
- Discuss the benefits and concerns of implementation of biosimilars into practice

Introduction to Biosimilars

What is a biologic?

- Large, complex proteins that are produced in living systems
- Wide range of products including vaccines, blood and blood components, allergenics, somatic cells, gene therapy, tissues, and recombinant therapeutic proteins
- Biologic reactions are variable and yield heterogenous products

Drugs. 2017 Jun;77(9):985-997.

What is a biosimilar?

- The FDA defines a biosimilar as:
  - "A biosimilar product is a biological product that is approved based on a showing that it is highly similar to an FDA-approved biological product, known as a reference product, and has no clinically meaningful differences in terms of safety and effectiveness from the reference product."

FDA. Information on Biosimilars. 2016

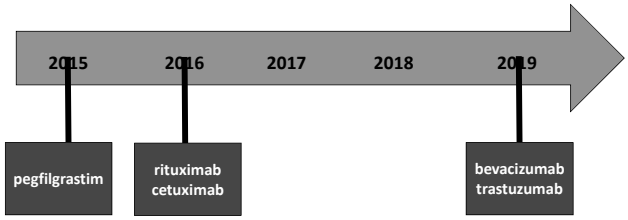
Characteristic	Nonbiologic Generic	Biologic	Biosimilar
Size	Small	Large	
Molecular weight	<10000 Da	200-100 times the size of a small molecule	4000 to >14000 Da
Structure	Simple to relatively simple	Complex	Potentially have structural variations but are designed to be highly similar to their biologic reference product
Manufacturing	Predictable and bioequivalent to the brand name	Piece of DNA added to a cell; a protein is generated and becomes the biologic	Stepwise process to make a similar compound
Immunogenicity	Low potential	High potential	Immunogenicity to the biosimilar is not increased relative to the reference product
Approval Requirements	Small clinical trials in healthy volunteers	Standard FDA guidelines	Large clinical trials; development of a biosimilar must include ≥ 1 clinical study; licensure pathway for a biosimilar is an abbreviated pathway

JAMA Oncol. 2017 Jul 20. doi: 10.1001/jamaoncol.2017.2004. [Epub ahead of print]

Biosimilar Medications Approved in the US

Biosimilar Product	Date of Approval
filgrastim-sndz/ Zarxio	March 6, 2015
infliximab-dyyb/ Inflectra	April 5, 2016
etanercept-szzs/ Erelzi	August 30, 2016
adalimumab-atto/ Amjevita	September 23, 2016
infliximab-dyyb/ Renflexis	April 24, 2017

Oncology Biologic Patent Expiration



Cost of Cancer Care

- 18.1 million cancer survivors predicted in 2020
  - 30% more than 2010
- $174 billion projected costs for 2020
  - $157 billion in 2010
- Biologics accounted for 32% of $9.5 billion Medicare Part B drug spending in 2005 and by 2014 they represented 62% of $18.5 billion

National Cancer Institute. https://costprojections.cancer.gov/
JAMA Oncol. 2017 Jul 20. doi: 10.1001/jamaoncol.2017.2004. [Epub ahead of print]

Biosimilars and Cost Savings

- Biosimilars are expected to decrease costs by ~30%
- One review projected that biosimilars will lead to a $44.2 billion reduction in drug spending over a 10 year span (2014-2024)
- Factors that can affect cost savings
  - No interchangeable status or automatic substitution
  - Reimbursement concerns
  - Slow adoption of new biosimilar agents

Mulcahy AW, Predmore Z, Mattke S. The cost savings potential of biosimilar drugs in the United States. https://www.rand.org/content/dam/rand/pubs/perspectives/PE100/PE127/RAND_PE127.pdf Published 2014. Accessed February 16, 2017.

Reimbursement

- Health plans considering placing biosimilars on lower tiers, which could require biosimilar use prior to the reference biologic
- In physician office, fee-for-service payment based on average sale price plus 4.3%
- Medicare Part D likely to cover wholesale acquisition cost plus a surcharge

JAMA Oncol. 2017 Jul 20. doi: 10.1001/jamaoncol.2017.2004. [Epub ahead of print]

Regulatory Process for Biosimilar Approval

Legislation

- Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments) of 1984
  - Generic medication approval without studies that demonstrate safety and efficacy
- Biologics Price and Competition and Innovation (BPCI) Act of 2009
  - Amendment in the Affordable Care Act
  - Biologic medication can be deemed "biosimilar" if the medication is highly similar to an existing biologic product

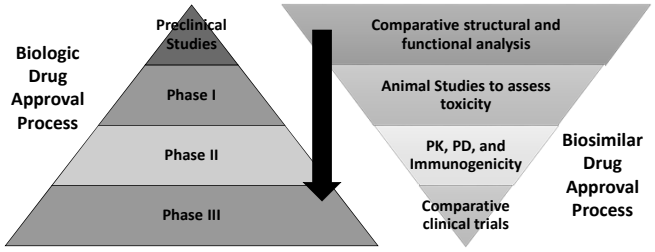
JAMA Oncol. 2017 Jul 20. doi: 10.1001/jamaoncol.2017.2004. [Epub ahead of print]

Small Molecules	Generics	Biologic License Application 351 (a)	Biosimilar
New Drug Application 505 (b)(1) or 505 (b)(2)	Abbreviated new drug application 505(j)		Biologics License Application 351 (k)*
Full report of safety and efficacy	Identical to an already approved product	Full reports of safety and efficacy investigations	Highly similar to a 351 (a) product
Two pathways dependent on right of reference	No safety or efficacy needed	Applicant has right of reference to essential investigations	Demonstration of absence of clinically meaningful difference

*If intent is for biosimilar product to be interchangeable then it must meet higher standards

FDA. Guidance for industry reference product exclusivity for biological products filed under section 351(a) of the PHS Act. 2014

Regulatory Requirements of Biologic Agents



FDA. Scientific considerations in demonstrating biosimilarity to a reference product: guidance for industry. 2015.

Naming of Biosimilar Medications

- At time of licensure a suffix is added consisting of four lowercase letters that will serve to distinguish the biosimilar agent

Suffixes SHOULD	Suffixes SHOULD NOT
Be unique	Be false or misleading
Be devoid of meeting	Include numerals or symbols
Be four lowercase letters of which three are distinct	Include abbreviations commonly used in clinical practice
Be nonproprietary	Contain or suggest any drug substance
Be attached to the core name with a hyphen	Look similar to or be capable of being mistaken for the name of a currently marketed product
Be free of legal barriers that would restrict its usage	Be similar to any FDA assigned non-proprietary name suffix

FDA. Nonproprietary naming of biological products: guidance for industry. 2017.

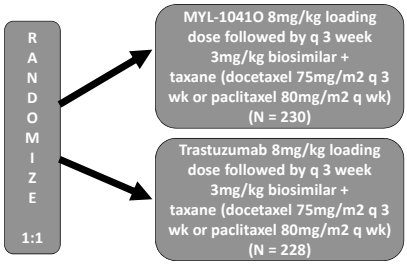
Immunogenicity

- Immune response to biologic mediations may affect safety and efficacy of patients
- Immunological based adverse events could include anaphylaxis, cytokine release syndrome, or neutralization of endogenous proteins
- Evaluation includes assays for anti-drug antibody, product specific sampling, comparative immunogenicity studies and postmarketing surveillance

FDA. Immunogenicity Assessment for Therapeutic Protein Products. Guidance for Industry . 2014.

HERITAGE Study: Trastuzumab Biosimilar (MYL-1041O)

- Study Population
  - ERBB2-positive metastatic breast cancer
  - ECOG PS 0-2
  - Normal LVEF
- Primary Endpoint
  - ORR



JAMA. 2017 Jan3;317(1):37-47

HERITAGE Study: Outcomes

- **Primary Endpoint (24 week follow-up)**

Study Arm	ORR	Confidence Interval
MYL-1401O + taxane	69.6%	(95% CI, 62.62%-75.51%)
trastuzumab + taxane	64%	(95% CI, 57.81%-70.26%)

- **Secondary Endpoints (48 week follow-up)**

Study Arm	Time to Tumor Progression	Progression-Free Survival	Overall Survival
MYL-1401O + taxane	41.3%	44.3%	89.1%
trastuzumab + taxane	43%	44.7%	85.1%

JAMA. 2017 Jan3;317(1):37-47

HERITAGE Study: Adverse Events

- **Adverse Events**

Adverse Event (Grade 4)	MYL-1401O + Taxane	Trastuzumab + Taxane
Neutropenia	27.5%	25.2%
Neutropenic Fever	4.5%	4.1%
Leukopenia	1.6%	4.9%
Pneumonia	1.6%	2%

- **LVEF**
  - Baseline LVEF for the biosimilar arm (64%) and trastuzumab arm (63%) at 24 weeks changed a median of -1% in both groups

JAMA. 2017 Jan3;317(1):37-47

HERITAGE Study: PK/PD and Immunogenicity

- PK/PD
  - Cmin, Cmax, AUC were similar in both arms of the study
- Immunogenicity

Study Arm	Antidrug Antibody Rate	Median Titer
MYL-1401O + taxane	2.4%	2.5
trastuzumab + taxane	2.8%	2.3

JAMA. 2017 Jan3;317(1):37-47

HERITAGE Study

- MYL-1401O and trastuzumab had similar overall response rates at 24 weeks
- Secondary outcomes supported equivalence
- Adverse events were similar
- Immunogenicity was low
- Long term data needed to evaluate safety and outcomes

JAMA. 2017 Jan3;317(1):37-47

Evaluation of the Data and Implementation in Practice

Interchangeability

- Interchangeability means the biosimilar "can be expected to produce the same clinical result as the reference product in any given patient"
- Risk of switching between products is not greater than using reference product consistently
- FDA guidance varies based on complexity of the biosimilar
- Submission of switching studies between biosimilar and reference product
- No biosimilar in the US has interchangeable status

Ann Pharmacother. 2017 Jul;51(7):590-602.

Illinois State Law

- Pharmacists can substitute biosimilars for biologics and vice versa
  - FDA must designate the biosimilar as interchangeable
  - Physicians may prohibit substitution
- Prescribers must be notified of substitutions within 5 days
  - Prescribers do not need to be notified if the substitution continues in a refill
- Patients must be notified of the substitution
  - No requirements for counseling
- Records of the substitution must be kept for 5 years
- The state board must maintain a list of interchangeable biologics on their website

Extrapolation of Indications

- FDA may extrapolate to an indication not studied by the biosimilar but has been approved for the reference product
- Biosimilar should demonstrate the same mechanism of action, PK, and biodistribution in the extrapolated indication
  - Varies on complexity of the medication
- Can lead to reduced cost to patients and payers
  - 20% reduction in the price of 5 off-patent pharmaceuticals could result in 9-12 billion savings over 10 years

Crit Rev Oncol Hematol. 2016 Aug;104:98-107.

Tbo-filgrastim post Stem Cell Transplant

- Retrospective chart review of 182 autologous stem cell transplant for multiple myeloma
  - 91 patients received filgrastim post transplant and 91 patients received tbo-filgrastim

Outcomes	Tbo-filgrastim	Filgrastim
Neutrophil engraftment (median days)	13	12
Hospital length of stay (median days)	16	16

- Safety profiles were similar between agents

Clin Transplant. 2015 Dec;29(12):1128-32.

Principles for Extrapolation

Factors
Clinical experience
Mechanism of Action in each indication
Target receptors involved
Differences in safety/immunogenicity profile between therapeutic indications
Degree to which functional moieties of the molecule can be analytically characterized and compared

Data Required for Regulatory Decision
Comparability exercise (i.e. PK/PD similarities)
Uncertainties – analytical or functional assays
Acceptable safety profile
Immunogenicity evaluation
Extrapolation only possible from high to low risk patient populations and settings

Blood. 2014 Nov 20;124(22):3191-6

Pharmacovigilance

- Monitoring of all biologics following approval is vital
- One example includes increased rates of antibody-mediated pure red cell aplasia (PRCA) observed in Europe between 1998 and 2004 secondary to epoetin manufacturing
- Safety monitoring of biosimilars includes voluntary reporting of adverse events and medication errors to the manufacturer or FDA

Cancer Med. 2014 Aug;3(4):889-99

Summary

- Biosimilar agents are biologic drugs that are highly similar to an FDA approved biologic agent known as the reference product
- Application for biosimilar evaluation should be filed under the Biologics License Application 351 (k) and includes information on analytical data, PK/PD, immunogenicity data, and comparative evaluations
- Biosimilar medications may reduce costs of biologics by ~30%
- Interchangeability and extrapolation remain points of concern in the United States and require evaluation of the totality of evidence in order to make the decision

Which of the following questions regarding biosimilars is true?

A. A biosimilar is a biologic product that is highly similar to an FDA approved reference biologic product

B. Biosimilar legislation stemmed from the Hatch-Waxman Amendment

C. Manufacturing of a biosimilar is predictable and bioequivalent to the reference biologic product

D. All of the above

Which of the following is NOT a requirement for review when evaluating a biosimilar?

A. Analytical Structure Review

B. Switching studies between biosimilar medications and the reference product

C. Pharmacokinetic and Pharmacodynamic Data

D. Immunogenicity

How many biosimilars have interchangeable status in the United States?

A. 0

B. 1

C. 3

D. 4

Which of the following is NOT a rule in Illinois with regards to biosimilar medications?

A. Prescribers must be notified of substitutions within 5 days

B. Illinois requires FDA interchangeable status in order to substitute a biologic with a biosimilar

C. Patients must be notified about the substitution and pharmacists must complete a biosimilar counseling checklist with each patient

D. Records must be maintained for 5 years

Which of the following are concerns for using biosimilars at this time?

A. Inappropriate extrapolation leading to lack of efficacy

B. Increased risk of immunogenicity leading to safety concerns

C. Lack of insurance reimbursement

D. All of the above

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