ADOPTION OF BIOSIMILARS:
KEY CONSIDERATIONS FOR INSTITUTIONS

A presentation for HealthTrust Members
June 5, 2019

Amar Saini, PharmD, MHS
PGY-1 Pharmacy Resident
Atlantic Health System

DISCLOSURES

- The presenter has no financial relationships with any commercial interests pertinent to this presentation.

- This program may contain the mention of drugs or brands presented in a case study or comparative format using evidence-based research. Such examples are intended for educational and informational purposes and should not be perceived as an endorsement of any particular supplier, brand or drug.

LEARNING OBJECTIVES: PHARMACISTS

- Evaluate the difference between biosimilars and generics
- Describe the FDA approval process for biosimilars
- Recall the changes made by Centers for Medicare & Medicaid Services (CMS) for the reimbursement of biosimilars
- Summarize key considerations for P&T committee members in evaluating biosimilars for formulary inclusion
- Explain operational challenges related to implementing biosimilars

LEARNING OBJECTIVES: PHARMACY TECHNICIANS

- Summarize key considerations for P&T committee members in evaluating biosimilars for formulary inclusion
- Explain operational challenges related to implementing biosimilars

INTRODUCTION TO BIOLOGICS

Biologics are large, complex molecules produced via biotechnology in a living system such as microorganism, plant cell or animal cell

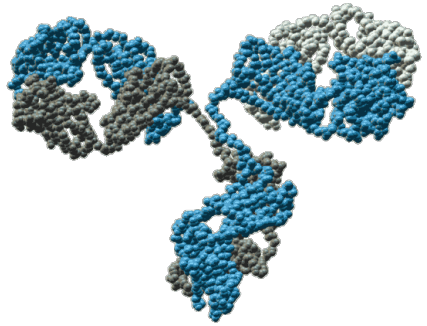
Types of biological products approved in the United States are therapeutic proteins, monoclonal antibodies, vaccines

There is inherent variation in manufacturing and characterizing these products due to complex process in production

Source: Retrieved from www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products

COMPARISON

	Small Molecule Drug	Biologic Agent
Entity	Chemical	Protein
Structure	Small, well characterized	Large, heterogeneous
Stability	Relatively stable	Vulnerable to environmental factors
Mode of administration	Enteral	Usually require parenteral
Manufacturing process	Predictable and precise method; Identical copies in batches	Living cell-based complex technology; Batch to batch variation; Sensitive to storage and handling
Immunogenicity	Low	High



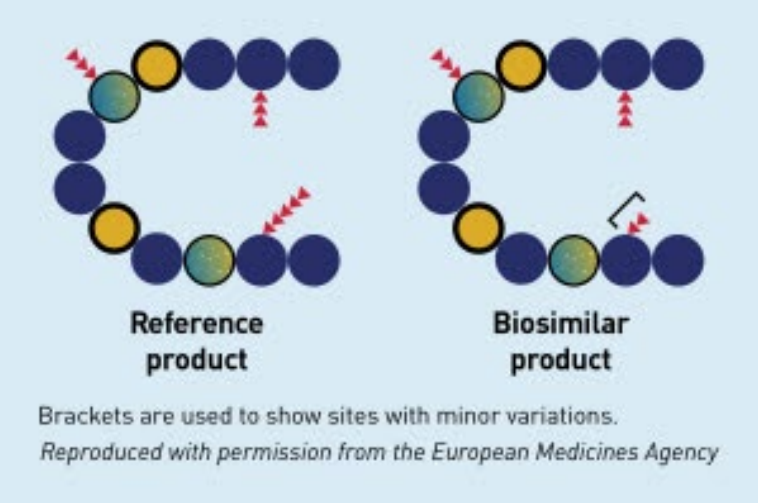
Source: Hoffman et al. ASHP. 2013

KEY TERMINOLOGIES

Reference Product	• Also known as the originator product which is already approved by FDA • Biosimilars are compared against reference product
Biosimilar	• Highly similar product which has no clinical meaningful differences from the reference product
Interchangeable	• Biosimilar products that meets additional requirements i.e. crossover-studies, post marketing surveillance data

Source: Retrieved from www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products

WHAT DOES IT MEAN TO BE "HIGHLY SIMILAR"?

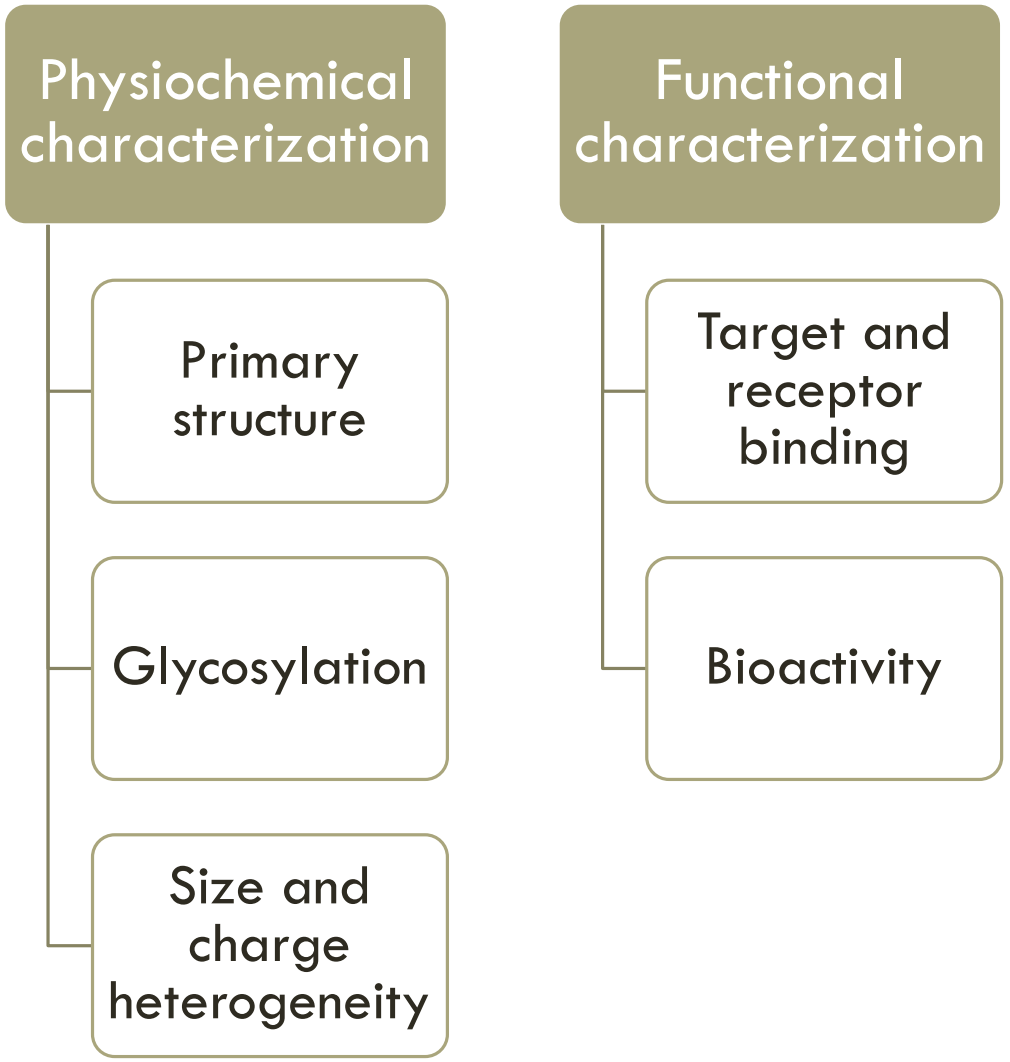


- Minor differences between the reference and its biosimilar
  - These difference are clinically inactive components which are acceptable as per the FDA
- Structure and function of both the reference product and the proposed biosimilar are extensively analyzed, referred as **analytical characterization**
- Analytical characterization reduces the burden to perform large clinical trials

Source: Retrieved from www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products

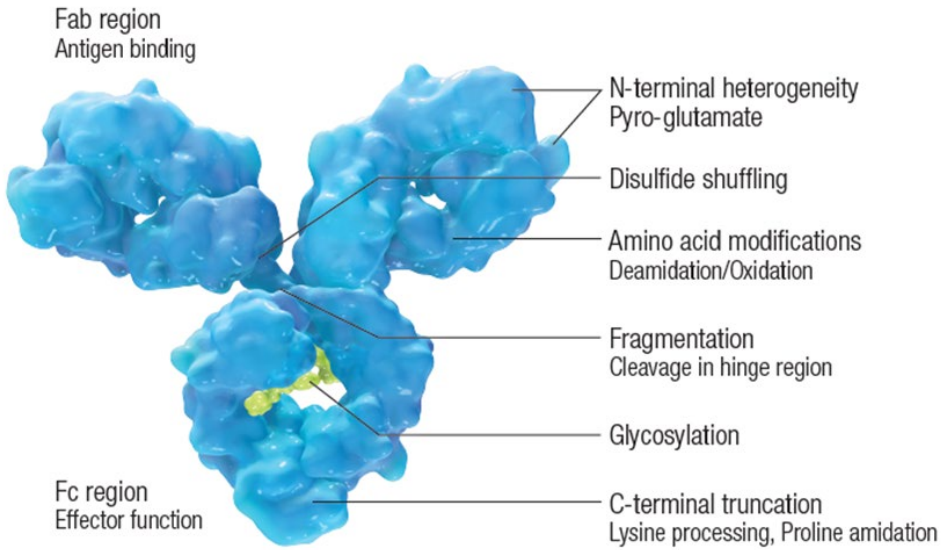
AIM OF ANALYTICAL CHARACTERIZATION

Investigate structural and functional elements



Source: Retrieved from www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval

WHY IS ANALYTICAL CHARACTERIZATION IMPORTANT?



Structural heterogeneity may compromise:

- Mechanism of action
- Pharmacokinetics
- Effector functions
- Immunogenicity
- Ligand binding

Source: Retrieved from www.amgenbiosimilars.com/pdfs/developing-biosimilars-the-process-and-quality-standards.pdf

ANALYTICAL CHARACTERIZATION: KEY POINTS

There is no specific types of analyses or assays for evaluating all biologics

The selection of analyses is dependent upon the properties of the reference product

Criteria for demonstrating similarities will vary from product to product

Source: Hung et al. JMCP. 2017

WHAT DOES IT MEAN TO HAVE "NO CLINICALLY MEANINGFUL DIFFERENCES"?

No clinical meaningful differences from the reference product in terms:

- Safety
- Purity
- Potency

Demonstrated primarily through human pharmacokinetic and pharmacodynamic studies

An assessment of clinical immunogenicity

Additional clinical studies if needed

Source: Retrieved from www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products

WHAT IS AN INTERCHANGEABLE PRODUCT?

Switching study or studies	Evaluate the risk, in terms of safety and potential decreased in efficacy, of alternating or switching between the products	Able to substitute for the reference product without consulting with the prescriber
	Same clinical results as the reference product in any given patient	

Source: Retrieved from www.fda.gov/drugs/biosimilars/prescribing-biosimilar-and-interchangeable-products#standards

WHY BIOSIMILARS?

U.S. spending on prescription drugs continues to rise

The increase in use of specialty drugs including biologics is one of the main drivers of spending growth

Biologics alone accounted for 38 percent of U.S. prescription drug spending

Substantial cost saving opportunities as the reference products come off patents

Estimated potential savings in the U.S. from just 11 biosimilars over the time period from 2014 to 2024 could be $250 billion

Source: Hung et al. JMCP. 2017

- Passed as part of the Affordable Care Act that President Obama signed into law on March 23, 2010
- Created an abbreviated licensure pathway for biosimilar products
- Intended to promote competition among pharmaceutical companies to lower prices and potentially increase access to medications

BIOLOGICS PRICE COMPETITION AND INNOVATION ACT OF 2009

Source: Hung et al. JMCP. 2017

MEET FDA STANDARDS FOR APPROVAL PROCESS

ARE MANUFACTURED AT FDA-LICENSED FACILITIES

ARE TRACKED AS PART OF POST-MARKET SURVIVALLENCE TO ENSURE CONTINUED SAFETY

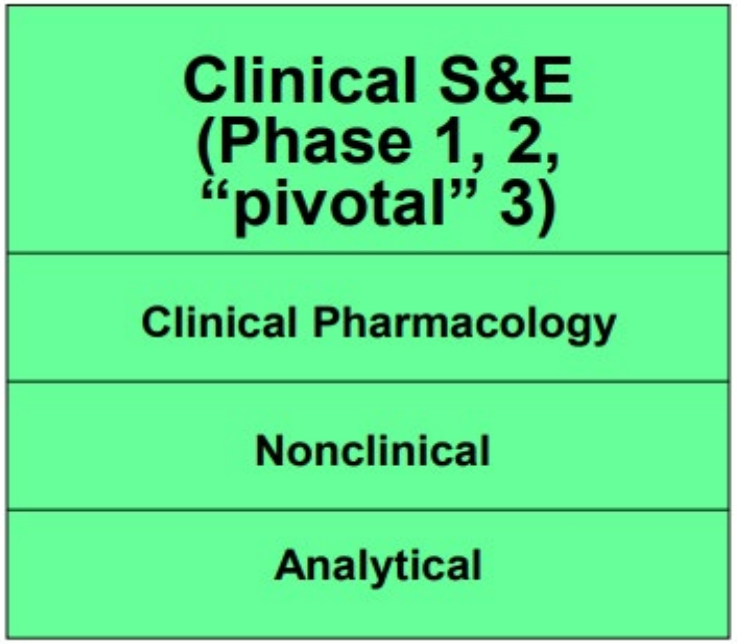
FDA APPROVAL CRITERIA FOR BIOSIMILARS

Source: Hung et al. JMCP. 2017

COMPARISON OF APPROVAL PROCESS

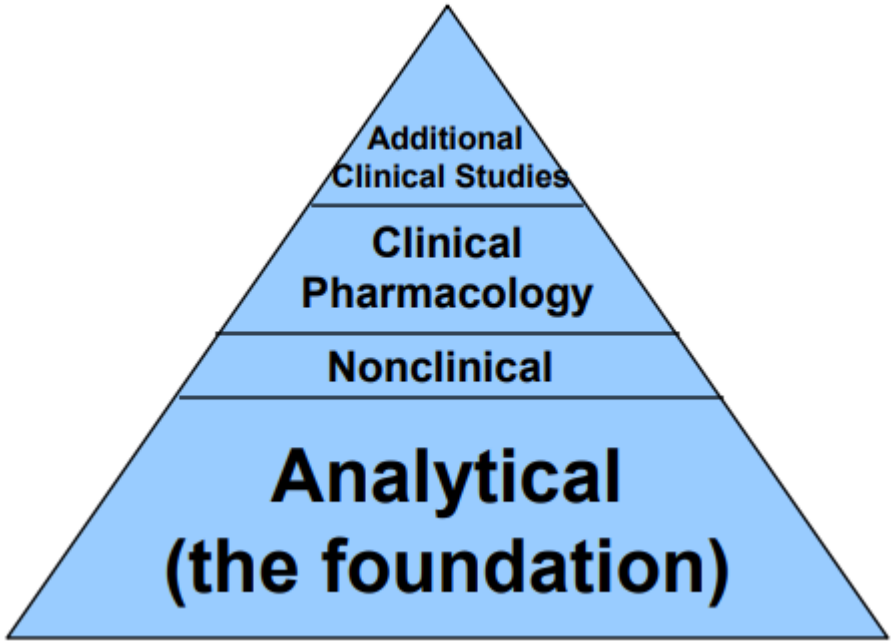
ORIGINATOR

- Development program, 351(a)
- Goal is to establish safety and effectiveness of the new product



BIOSIMILAR

- Development program, 351(k)
- Totality of the evidence to demonstrate biosimilarities



Source: Hung et al. JMCP. 2017

DIFFERENCE IN DEVELOPMENT TIME & COST BETWEEN GENERIC & BIOSIMILAR PRODUCTS

TABLE 1 Differences in Development Time and Cost Among Chemical, Generic, Biological, and Biosimilar Drugs

	Chemical Drugs[33]	Generic Drugs[33]	Biological Drugs[34,35]	Biosimilar Drugs[36]
Development time	7-10 years	1-3 years	10-15 years	8-10 years
Development cost	~$800M	$1M-2M	$1,200M-2,500M	$100M-200M

Note: Costs are in U.S. dollars.

Biosimilars require extensive analytical data to demonstrate high similarity, which may prolong development time and increase cost for biosimilars

Source: Hung et al. JMCP. 2017

TIME LINE & LOE

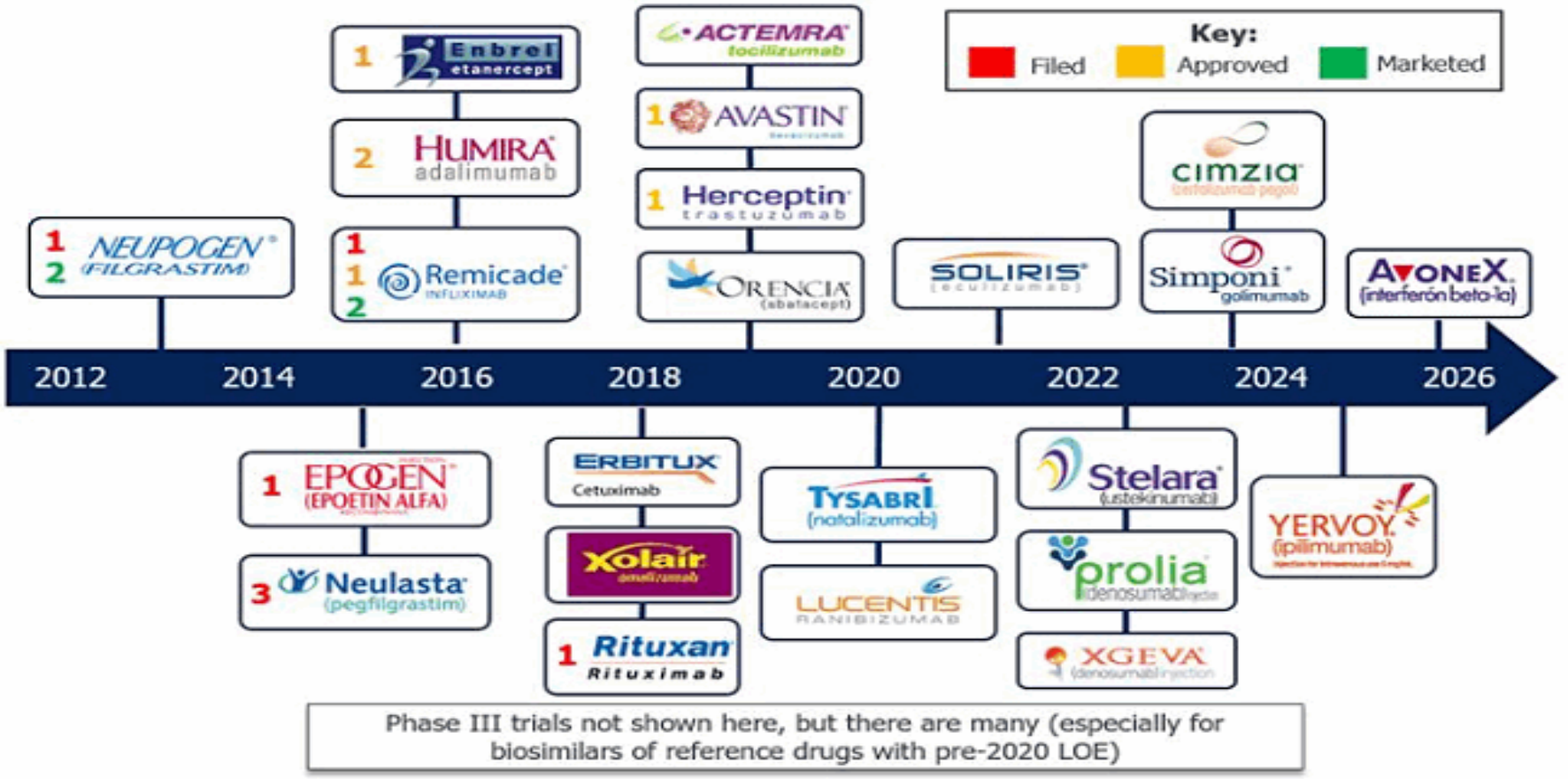


Figure 1: *Loss of exclusivity (LOE) and biosimilar entry timeline — LOE is approaching for many biologics, priming the market for more biosimilar entry.*

Source: Danosi et al. Biosimilar Development. 2017

CURRENT FDA-APPROVED BIOSIMILAR PRODUCTS

Zarxio (filgrastim-sndz) March 2015	Inflectra (infliximab-dyyb) April 2016	Erelzi (etanercept-szzs) August 2016	Amjevita (adalimumab-atto) September 2016	Renflexis (infliximab-abda) May 2017	Cyltezo (adalimumab-adbm) August 2017
Mvasi (bevacizumab-awwb) September 2017	Ogivri (trastuzumab-dkst) December 2017	Ixifi (infliximab-qbtx) December 2017	Retacrit (epoetin alfa-epbx) May 2018	Fulphila (pegfilgrastim-jmdb) June 2018	Nivestym (filgrastim-aafi) July 2018
Hyrimoz (adalimumab-adaz) October 2018	Udenyca (pegfilgrastim-cbqv) November 2018	Truxima (rituximab-abbs) November 2018	Herzuma (trastuzumab-pkrb) December 2018	Ontruzant (trastuzumab-dttb) January 2019	Trazimera (trastuzumab-qyyp) March 2019
		Eticovo (etanercept-ykro) April 2019			

Source: Retrieved from www.fda.gov/drugs/biosimilars/biosimilar-product-information

PHARMACIST ASSESSMENT QUESTION #1:
WHAT IS THE FOUNDATION OF DEMONSTRATING BIOSIMILARITY?

A. Animal studies
B. Clinical studies
C. Analytical characterization
D. Post-marketing surveillance

PHARMACIST RESPONSE #1:
WHAT IS THE FOUNDATION OF DEMONSTRATING BIOSIMILARITY?

A. Animal studies
B. Clinical studies
C. **Analytical characterization**
D. Post-marketing surveillance

PHARMACY TECHNICIAN ASSESSMENT QUESTION #1:
BIOLOGICAL PRODUCTS ARE PRODUCED IN WHICH OF THE FOLLOWING?

A. Bacteria
B. Viruses
C. Plant
D. Animal cells
E. Human cells
F. All of the above

PHARMACY TECHNICIAN RESPONSE #1: BIOLOGICAL PRODUCTS ARE PRODUCED IN WHICH OF THE FOLLOWING?

A. Bacteria
B. Viruses
C. Plant
D. Animal cells
E. Human cells
F. **All of the above**

KEY CONSIDERATION FOR UTILIZING BIOSIMILARS

Clinical

Product

Institutional

CLINICAL CONSIDERATION

CLINICAL CONSIDERATION: INDICATIONS

- The indications for an approved biosimilar may not include all the indications that the original product holds
- Indications are dependent upon the sponsor's application and whether the data from clinical trials can be extrapolated to multiple indications
- In addition, the BPCI act requires further rigorous evaluation for a biosimilar to be labeled "interchangeable"
- However, FDA is allowing hospitals or health systems to have the authority to designate interchangeable status and off-label use of biosimilars within their institution
- The pharmacy and therapeutic (P&T) committee will play a key role in performing the evaluation for interchangeability or auto-substitution and off-label use

Sources: Lucio et al. Am J Health Syst Pharm. 2014
Hoffman et al. ASHP. 2013
Ventola et al. P&T. 2015

CLINICAL CONSIDERATION: EFFICACY

- Evaluate the totality of evidence supporting the FDA's approval of a biosimilar especially, when considering additional indications
- Pre- and post-approval clinical data should be evaluated
- Switch data or cross-over studies can be beneficial for evaluating efficacy and safety
- Since approval of biosimilars heavily rely on analytical data, institution may need to acquire more expertise in the laboratory methods and analytical techniques

Sources: Lucio et al. Am J Health Syst Pharm. 2014
Hoffman et al. ASHP. 2013
Ventola et al. P&T. 2015

CLINICAL CONSIDERATION: SAFETY

- **Immunogenicity reaction** is one of the major concern when switching between original
  - It is the immune response of the host against the biosimilar
- Immunogenicity of a biosimilar can theoretically differ from their reference product
- Subtle changes in the protein structure or delivery of a biosimilar (e.g.. dose, dosing regimen, route of administration, or vehicle) can potentially affect the level of immunogenicity
- Other factors that can affect immunogenicity include impurities, and immune status of the patient

Sources: Lucio et al. Am J Health Syst Pharm. 2014
Hoffman et al. ASHP. 2013
Ventola et al. P&T. 2015

CLINICAL CONSIDERATION: SAFETY

- When reviewing literature in regards to the safety of the proposed biosimilar it is important to evaluate the difference in incidence of:
  - Infusion reaction—safety
  - Neutralizing antibodies—efficacy
- Clinical data from international sources should be utilized when evaluating safety and efficacy
  - Post-approval data from international sources
  - Cross-over studies

Sources: Lucio et al. Am J Health Syst Pharm. 2014
Hoffman et al. ASHP. 2013
Ventola et al. P&T. 2015

PRODUCT CONSIDERATION

PRODUCT CONSIDERATION: NAMING CONVENTION

- For each reference product and it's related biosimilar product's naming convention will consist of:
  - non-proprietary name or the core name + an FDA designated, distinguishable suffix of four letters
- Example:
  - Reference product:
    - Brand name: Herceptin®
    - Core name: Trastuzumab
  - Biosimilar product:
    - Brand name: Trazimera®
    - Core name with four letters: Trastuzumab-qyyp

Recent FDA update: All biologics (Original and biosimilar) will be distinguished with 4 letter suffix.

Source: Ventola et al. P&T. 2015

PRODUCT CONSIDERATION: NAMING CONVENTION

Institution must evaluate how the biosimilar names will affect their electronic medical system

How will they be tracked under their current computer system

Utilizing NDC data for barcoding/scanning can be one of the ways to mitigate risk

Other strategies may need to be evaluated for institutions without barcoding technology in order to prevent medication related errors

Source: Ventola et al. P&T. 2015

PRODUCT CONSIDERATION: PACKAGING, LABELING & STORAGE

Product labeling and packaging should be distinct and clear to allow differentiation between the two products (a biosimilar and the reference product)

Evaluate differences in shelf life, storage temperature, light sensitivity, and routes of administration

Separate stocking location should be considered in order to avoid dispensing errors

Review and compare preparation time and techniques between the two products to prevent compounding errors

Source: Ventola et al. P&T. 2015

INSTITUTIONAL CONSIDERATION

INSTITUTIONAL CONSIDERATIONS: SUBSTITUTIONS & INTERCHANGEABILITY

- Health systems can create policies around formulary inclusion for a biosimilar to be considered for substitution
- P&T committee members will need to conduct a thorough risk-benefit evaluation
- Criteria to consider for permitting therapeutic substitution:
  - Therapeutic and dose equivalence, efficacy and safety risks when switching products
  - Cost comparison between the two products
  - Ability to opt out in specific circumstances
  - Ability to monitor and assess efficacy and safety outcomes

Source: Ventola et al. P&T. 2015

INSTITUTIONAL CONSIDERATIONS: REIMBURSEMENT

- Whole sale acquisition cost (WAC) is a price set by the manufacturer
- WAC for biosimilars are typically priced at ~15% reduction compared to the reference product
- Most distributors, group purchasing organizations (GPOs) and providers negotiate the actual purchase price
- Payers generally do not reimburse at WAC either except in the first 2 – 3 quarters, post the biosimilar launch

Source: Danosi et al. Biosimilar Development. 2017

Biosimilar reimbursement =
Biosimilar ASP + 6% of the reference product's ASP

CMS reimbursement is based on average sales price (ASP) of the biosimilar product

In the past, all biosimilars were grouped under one HCPCS code, which meant they could not compete against each other and could only compete against the reference product

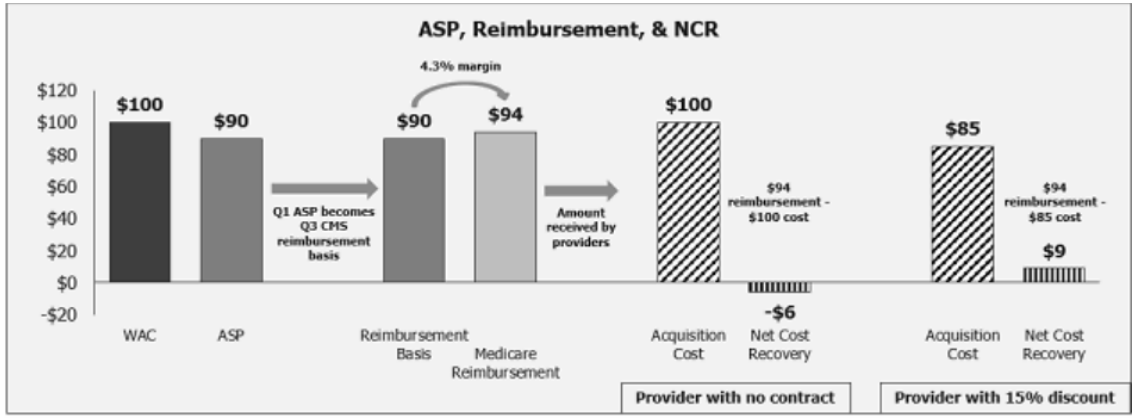
CMS changed their reimbursement plan in order to encourage price competition among biosimilars of a reference product

As of 2018, each biosimilar of a reference product receives a unique HCPCS code

INSTITUTIONAL CONSIDERATIONS: MEDICARE REIMBURSEMENT

Average selling price (ASP) calculation

Source: Danosi et al. Biosimilar Development. 2017



NCR = Reimbursement - Purchase cost of drug

NCR = (ASP + 4.3%) - (WAC - Manufacturer discounts)

- Net cost recovery (NCR) equation is the difference between the price paid for administered biosimilar and the reimbursement received from the payer
- Acquisition cost varies across providers

INSTITUTIONAL CONSIDERATIONS: MEDICARE REIMBURSEMENT

NCR calculation example

Source: Danosi et al. Biosimilar Development. 2017

INSTITUTIONAL CONSIDERATIONS: TRANSITION OF CARE

- As the prices of biosimilars decreases, payers will likely provide incentives for its use to reduce or control cost
- This could result in higher co-payments or coinsurance premiums for use of the reference product
- Manufacturers of original product could offer significant discounts to encourage the health systems to continue using their product
- This may divert financial burden to patients when they are discharged out of hospital

Source: Ventola et al. P&T. 2015

INSTITUTIONAL CONSIDERATIONS: PHARMACOVIGILANCE

- Clinical studies for biosimilars are not powered to thoroughly assess the side-effect profile and immunogenicity
- These are short-term studies which may not reveal all the potential adverse events of a biosimilar
- Pharmacovigilance maybe necessary to implement in order to track immunogenicity reactions and other unexpected side effects related to biosimilar use
- Post-marketing surveillance will be beneficial in monitoring diverse patient populations and off-label uses

Source: Ventola et al. P&T. 2015

INSTITUTIONAL CONSIDERATIONS: PHARMACOVIGILANCE

- Strategies for implementing post-marketing surveillance:
  - Patient registries and prospective or retrospective observational review
  - Risk evaluation and mitigation strategies (REMS)
  - MedWatch reports to the FDA
- In order to trace biosimilars, they need to be identified with unique nonproprietary names and NDC or billing codes in accounting records and/or electronic health records

Source: Ventola et al. P&T. 2015

INSTITUTIONAL CONSIDERATIONS: COST

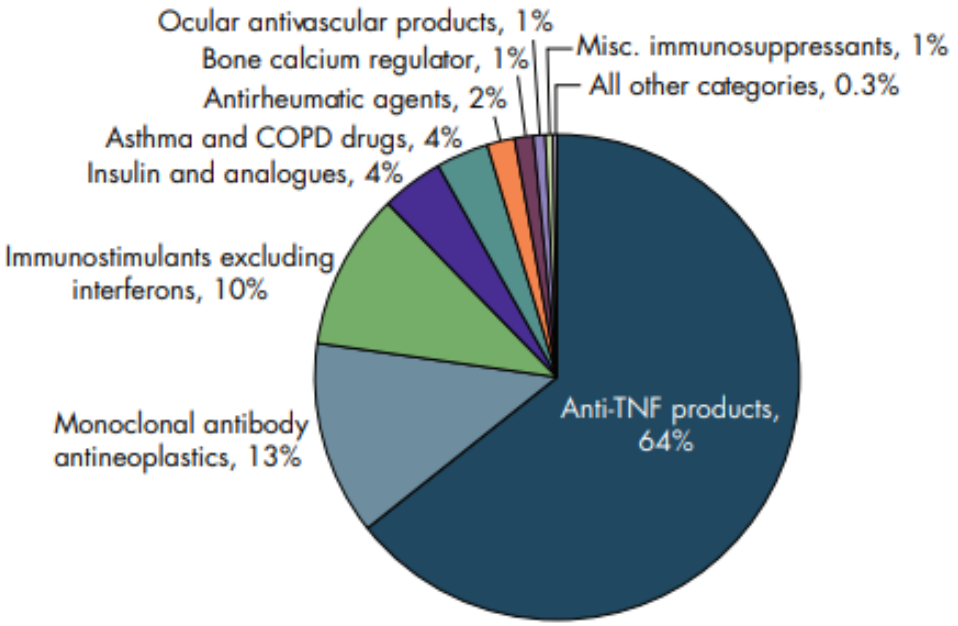
- Due to the high cost associated with research and development of biosimilars it is expected that they will be discounted by only 15% to 35%
- Discounts should increase as biosimilars gain market share; however, it will vary across biologic classes
  - It is dependent on sales, the timing of biosimilar entry and the degree of competition
- Cost-minimization analysis should be conducted prior to adding a biosimilar to the formulary
- It should also be vetted through a cost-control method such as prior authorization

Source: Ventola et al. P&T. 2015

INSTITUTIONAL CONSIDERATIONS: COST

- The anti-TNF category has one of the largest biologic products by sales and available biosimilars
- It is predicted to have substantially cost-saving opportunities

Estimated Cost Savings, by Biologic Class



Source: Mulcachy et al. Rand Corporation. 2018

INSTITUTIONAL CONSIDERATIONS: PATIENT EDUCATION

Educate on the difference between generics and biosimilars

Advise patients on the pros and cons of being prescribed or switched to a biosimilar

Create educational materials for the patients for important topics, such as appropriate use, interchangeability and cost difference

Sources: Hoffman et al. ASHP. 2013
Ventola et al. P&T. 2015

ROLE OF A PHARMACIST

- Pharmacist can fill the knowledge gap by educating prescribers, nurses, and patients
- Identify potential disparities between a biosimilars and its reference product
- Evaluate the quality of crossover-studies for substitution
- Assist in formulary decision making process for inclusion of biosimilars
- Assist in implementation of pharmacovigilance programs

Sources: Hoffman et al. ASHP. 2013
Ventola et al. P&T. 2015

PHARMACIST ASSESSMENT QUESTION #2:
WHAT WERE THE MAJOR CHANGES MADE BY CMS FOR THE REIMBURSEMENT OF BIOSIMILARS IN 2018? (SELECT ALL THAT APPLY)

A. All the biosimilars for the same reference product will share a common HCPCS code

B. Each biosimilar of a reference product will have a specific HCPCS code

C. Medicare will reimburse based on biosimilar's own ASP + 6% of the reference product's ASP

D. Medicare will reimburse based on biosimilar's own WAC + 6% of the reference product's ASP

PHARMACIST RESPONSE #2:
WHAT WERE THE MAJOR CHANGES MADE BY CMS FOR THE REIMBURSEMENT OF BIOSIMILARS IN 2018? (SELECT ALL THAT APPLY)

A. All the biosimilars for the same reference product will share a common HCPCS code

B. **Each biosimilar of a reference product will have a specific HCPCS code**

C. **Medicare will reimburse based on biosimilar's own ASP + 6% of the reference product's ASP**

D. Medicare will reimburse based on biosimilar's own WAC + 6% of the reference product's ASP

PHARMACIST ASSESSMENT QUESTION #3: WHAT ARE SOME CRITERIA FOR A P&T COMMITTEE TO CONSIDER FOR PERMITTING THERAPEUTIC INTERCHANGEABILITY FOR A BIOSIMILAR?

A. Therapeutic and dose equivalence, efficacy and safety risks when switching products
B. Cost comparison between the two products
C. Ability to opt out in specific circumstances
D. Ability to monitor and assess efficacy and safety outcomes
E. All of the above

PHARMACIST RESPONSE#3:
WHAT ARE SOME CRITERIA FOR A P&T COMMITTEE TO CONSIDER FOR PERMITTING THERAPEUTIC INTERCHANGEABILITY FOR A BIOSIMILAR?

A. Therapeutic and dose equivalence, efficacy and safety risks when switching products
B. Cost comparison between the two products
C. Ability to opt out in specific circumstances
D. Ability to monitor and assess efficacy and safety outcomes
E. **All of the above**

PHARMACY TECHNICIAN ASSESSMENT QUESTION #2: SELECT THE CORRECT NAMING CONVENTION FOR PEGFILGRASTIM:

A. Pegfilgrastim-45db
B. Pegfilgrastim-4569
C. Pegfilgrastim-jmd
D. Pegfilgrastim-jmdb

PHARMACY TECHNICIAN RESPONSE#2: SELECT THE CORRECT NAMING CONVENTION FOR PEGFILGRASTIM:

A. Pegfilgrastim-45db
B. Pegfilgrastim-4569
C. Pegfilgrastim-jmd
D. **Pegfilgrastim-jmdb**  **Non-proprietary name + four letters**

ACKNOWLEDGEMENT

Christina Howlett, PharmD, BCOP

- Hematology/Oncology Clinical Pharmacy Specialist

Timothy Lise, PharmD, BCPS

- Manager, Clinical Pharmacy Services

THANK YOU!

Amar Saini, PharmD, MHS
amar.saini@atlantichealth.org