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Navigating Biosimilars

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Objectives

1. Define what biosimilars are from a manufacturing, regulatory and legal perspective
2. Recall the current oncology biosimilars approved in the United States of America
3. Apply understanding of biosimilars and their barriers to implement institutional processes for biosimilar integration

Acronyms

ASCO	American Society of Clinical Oncology
BPCIA	Biologics Price Competition and Innovation Act
EDTA	Ethylenediaminetetraacetic acid
DLBCL	Diffuse large-cell B-lymphoma
FDA	Food & Drug Administration
FL	Follicular Lymphoma
MDV	Multi-dose vial
NSCLC	Non-small-cell lung cancer
nsqNSCLC	Non-squamous NSCLC
ORR	Overall response rate
OS	Overall survival
PAP	Patient-assistance program
PD	Pharmacodynamics
PFS	Progression-free survival
PK	Pharmacokinetics
P&T	Pharmacy & Therapeutics Committee
R-CHOP	Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone regimen

Introduction to Biosimilars

Biologics & Biosimilars

- Biologics in general are large, complex molecules produced through biotechnology in a living system
- Biosimilars are a subset of biological medicines that are HIGHLY similar in structure and function to a reference (original) biologic product. This similarity is such that there are “no meaningful differences” between it and its brand name biologic

https://www.cancer.org/cancer/managing-cancer/treatment-types/biosimilar-drugs/what-are-biosimilars.html#:~:text=A%20biosimilar%2C%20or%20biosimilar,can%20work%20in%20many%20ways.

Biosimilars vs Generic Drugs

Biosimilars vs Generic Drugs	
Similarities	**Differences**
Both are tested and compared to a brand name drug in studies	Not an EXACT chemical copy
The reference brand name drugs have already been approved by the FDA	The FDA often needs more information from studies comparing a biosimilar to its original biologics than it needs from studies done on a generic drug
Both go through a shortened FDA review process compared to the reference product	Each have specific regulatory pathways for approval: 505(j) and 505(b)(2) –VS- 351(k)
Both are as safe and effective as their brand name drugs	Biosimilars require separate approval to be considered interchangeable with its brand name biologic, while generics can be automatically substituted for its brand name drug
Both might be less expensive than the reference product	

Biosimilars' Approval Qualifications

Study Type	Details	Sequence
Analytical tests to support approval	• Extensive analysis of biosimilar structure • Deviations from reference influence extensiveness of further studies • Biologic activity, potency, and mechanism of action are determined in vitro and in vivo	1
Animal studies to support approval	• Conducted to support the safety evaluation of the prospective biosimilar • Typically includes toxicity studies • Extensiveness depends on robustness of analytical studies	2
Clinical studies to support approval	• Usually required for complete pharmacologic profile • Human pharmacokinetics and pharmacodynamics • Immunogenicity • **Efficacy & safety studies comparing to reference product**	3

Biosimilars' Approval Qualifications

- "Extrapolation" of Data
  - Biosimilars can be approved for multiple indications simultaneously given that:
    - The reference product is indicated for said indications
    - There are no active market exclusivity periods for said indications
  - Manufacturer must provide adequate scientific justification
    - Totality of evidence
    - The clinical evidence is critical
    - A clinical trial compared to the reference product in a sensitive indication is typically required

Biosimilars & Interchangeability

- Definition: a biosimilar that meets additional requirements, supported by evidence, according to BPCIA
  - Additional requirements are:
    - Interchange/switch studies to show that an interchangeable product produces the same clinical result as the reference product in any given patient
    - If administered to a patient more than once, the risk in terms of safety and reduced efficacy of switching back and forth between an interchangeable product and a reference product will have been evaluated

Biosimilars & Interchangeability

- Reasoning:
  - Interchangeable biosimilars can be substituted without consultation of a prescriber (pending state laws)
  - 1st interchangeable product has 1 year of exclusivity

Current FDA-Approved Oncology Biosimilars

Reference	Biosimilar	Approval	Interchangeability	Deviations
Filgrastim	Filgrastim-sndz	Mar 2015	N	No vial formulation
	Filgrastim-aafi	Jul 2018	N	N/A
	Filgrastim-ayow	Feb 2022	N	N/A

Filgrastim-sndz [prescribing information]; September 2022

Filgrastim-aafi [prescribing information]; November 2021

Filgrastim-ayow [prescribing information]; April 2022

Current FDA-Approved Oncology Biosimilars

Reference	Biosimilar	Approval	Interchangeability	Deviations
Pegfilgrastim	Pegfilgrastim-jmdb	Jun 2018	N	No On-body formulation
	Pegfilgrastim-cbqv	Nov 2018	N	No On-body formulation* Has an autoinjector formulation
	Pegfilgrastim-bmez	Nov 2019	N	Coming off market
	Pegfilgrastim-apgf	Jun 2020	N	No On-body formulation
	Pegfilgrastim-pbbk	May 2022	N	No On-body formulation
	Pegfilgrastim-fpgk	Sep 2022	N	No On-body formulation

* = Onpro formulation to launch later this year per a recent clinical in-service

Pegfilgrastim-jmdb [product monograph]; March 2023
Pegfilgrastim-apgf [prescribing information]; March 2023.
Pegfilgrastim-cbqv [prescribing information]; March 2023.
Pegfilgrastim-pbbk [prescribing information]; May 2022.
Pegfilgrastim-bmez [prescribing information]; March 2021.
Pegfilgrastim-fpgk [prescribing information]; September 2022.

Current FDA-Approved Oncology Biosimilars

Reference	Biosimilar	Approval	Interchangeability	Deviations
Epoetin alfa	Epoetin alfa-epbx	May 2018	N	40,000 IU/mL contains phenylalanine

Reference	Biosimilar	Approval	Interchangeability	Deviations
Rituximab	Rituximab-abbs	Nov 2018	N	None
	Rituximab-pvvr	Jun 2019	N	None, but contains EDTA
	Rituximab-arrx	Dec 2020	N	None

Epoetin alfa-epbx [prescribing information]; April 2023.
Rituximab-abbs [prescribing information]; April 2023.
Rituximab-pvvr [prescribing information]; November 2021.
Rituximab-arrx [prescribing information]; June 2022.

Current FDA-Approved Oncology Biosimilars

Reference	Biosimilar	Approval	Interchangeability	Deviations
Bevacizumab	Bevacizumab-awwb	Sep 2017	N	None
	Bevacizumab--bvzr	Jun 2019	N	None, but contains EDTA
	Bevacizumab-maly	Apr 2022	N	None
	Bevacizumab-adcd	Sep 2022	N	None, but is not preservative-free

Bevacizumab-awwb [prescribing information]; February 2023
Bevacizumab-adcd [prescribing information];February 2023.
Bevacizumab-bvzr [prescribing information]; February 2023.
Bevacizumab-maly [prescribing information]; April 2022.

Current FDA-Approved Oncology Biosimilars

Reference	Biosimilar	Approval	Interchangeability	Deviations
Trastuzumab	Trastuzumab-dkst	Dec 2017	N	Also comes as 420 mg MDV, 1 as a vial itself and 1 coming with diluent
	Trastuzumab-pkrb	Dec 2018	N	Also comes as 420 mg MDV
	Trastuzumab-dttb	Jan 2019	N	Also comes as 420 mg MDV
	Trastuzumab-qyyp	Mar 2019	N	Also comes as 420 mg MDV
	Trastuzumab-anns	Jun 2019	N	Also comes as 420 mg MDV

Trastuzumab-dkst [prescribing information]; February 2021
Trastuzumab-qyyp [prescribing information]; November 2020.
Trastuzumab-pkrb [prescribing information]; May 2019
Trastuzumab-anns [prescribing information]; October 2019
Trastuzumab-dttb [prescribing information]; June 2021

Original Impetus for Biosimilars

- Original claim to fame
  - Biosimilars would decrease drug expenditures by being sold at lower prices than the reference biologic (currently 10.2 to 84.8% markoff), in turn causing price reductions in the reference biologic due to market competition
- Reality (for oncology)
  - In 2018, clinic expenditures for 3 key oncology therapeutics (bevacizumab, rituximab and trastuzumab) totaled approximately $7.7 billion
  - In 2019, after 4 biosimilars for bevacizumab, trastuzumab, and rituximab were launched, total expenditures decreased to $5.4 billion
  - In 2021, 10 biosimilars for these key biologics had reached the market, further decreasing expenditures for the reference products to $2.86 billion

Original Impetus for Biosimilars

- Reality (for oncology)
  - Despite the previous examples of price decreases, the main driving factors increasing oncology spending are:
    - The approval and release of novel small molecule and biologic products
    - Increased oncologic spending due to the continued use of immuno-oncology regimens that had accelerated approvals that were later rescinded
- Synopsis
  - **Biosimilars in the oncology realm DO help with cost savings. They HAVE NOT however, supported true reversal or a halting of increasing healthcare expenditures**

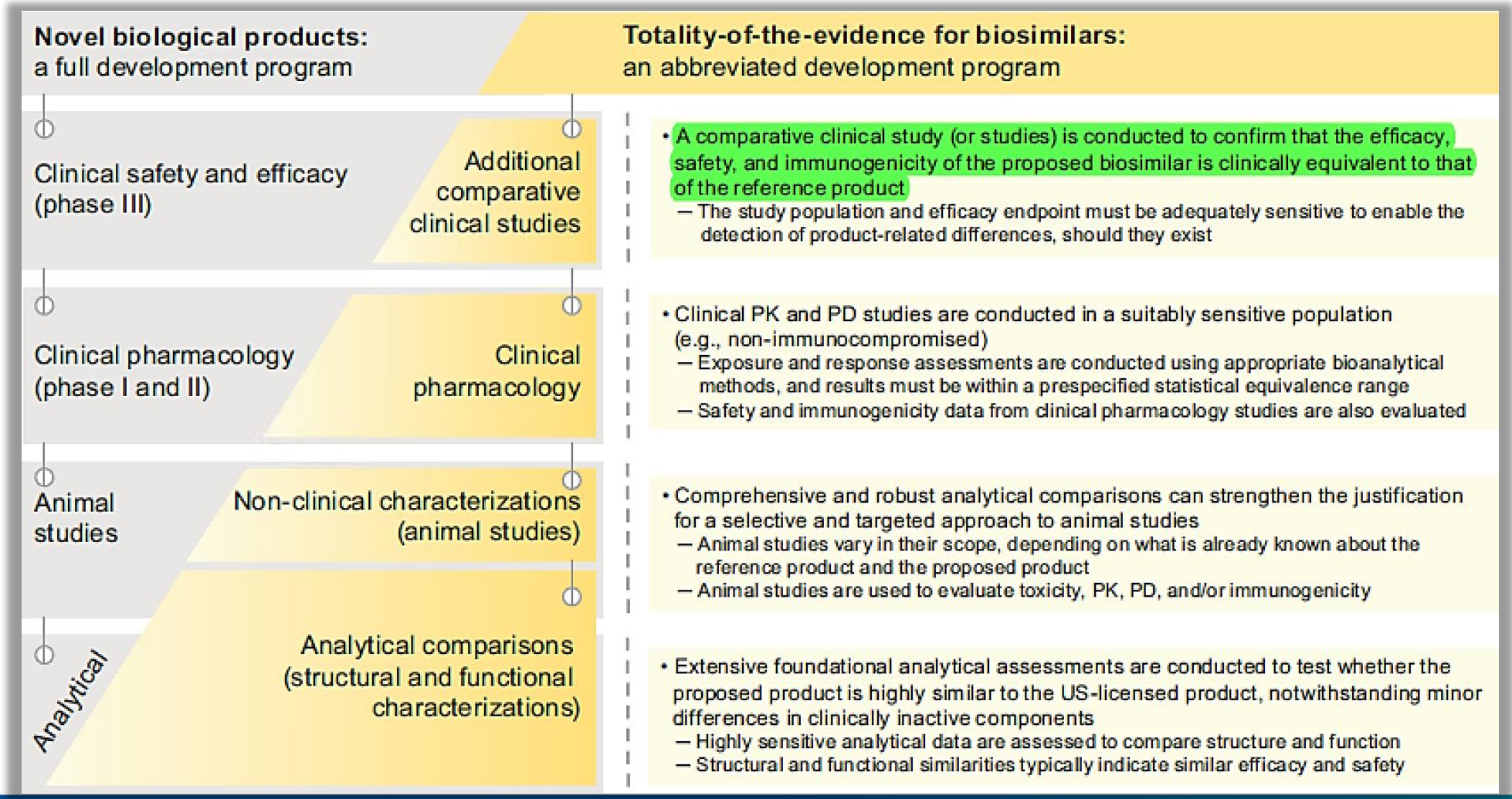
Tackling Barriers to Biosimilar Uptake

Barriers to Universal Adoption – Overview

- Biosimilar standards for efficacy & safety
- Interchangeability concerns
- Product availability, pricing, reimbursement & Payer preferences
- Formulary management

Rodriguez G et al. JCO Oncol Pract. 2023;19(7):411-20
Jinyang Y et al. BioDrugs. 2022;36:71-83
Greene L et al. J Manag Care Spec Pharm. 2019;25(8):904-12
Nabhan C et al. The Oncologist. 2018;23:1261-5
Shubow S et al. Clin Pharmacol Ther. 2023;113(1):37-49

Addressing Biosimilar Safety and Efficacy



Addressing Biosimilar Safety and Efficacy

- Virtually all of the currently marketed oncology biosimilars have been compared to their reference product in a clinical study
- **A note of confidence:**
  - Analytical and clinical pharmacology studies and results have so far never been refuted by clinical confirmatory studies

Addressing Biosimilar Safety and Efficacy

Biosimilar	Trial	Monotherapy/ Combo	Disease State	Endpoints
Bevacizumab-adcd	Verschraegen et al.	Combo	Recurrent or Stage IV NSCLC	ORR =42.4% vs 42.07% mPFS = 7.9 vs 7.2 months (p=0.37) mOS = 17.1 vs 15.6 months (p=0.6683)
Rituximab-abbs	Kwak et al.	Monotherapy	Newly diagnosed FL	ORR 88% vs 87% 2y PFS = 88% vs 83% 2y OS = 98% vs 98%
Trastuzumab-dkst	HERITAGE	Combo	Metastatic breast cancer	ORR = 69.6% vs 64% mPFS = 11.1 vs 11.1 months mOS = 35 vs 30.2 months (p=0.325)

All were compared to their respective reference products, and all first values (for endpoints) belong to the biosimilar

Addressing Biosimilar Safety and Efficacy

- Example of Real-World Evidence:
  - The **Dutch Cancer Registry** yielded positive real-world results regarding rituximab biosimilars vs the reference product
    - The study included 4429 patients with DLBCL – 876 in the biosimilar group and 3553 patients in the reference product group
    - All patients were treated with at least 1 cycle of R-CHOP from 2014-2018 and were analyzed for 3-year OS as the primary end point
    - **The study illustrated that the 3-year OS was 73% in both groups; this was the result after using multivariate Cox regression analysis accounting for sex, age, international prognostic index score, and number of R-CHOP cycles**

Brink M et al. Blood Adv. 2021;5(15):2958-2964.

Addressing Interchangeability

- Most state laws require almost uniformly that:
  - Pharmacists notify both the provider and patient that a substitution has been made
  - Pharmacist and prescriber retain records of substituted biologic medications
  - Legislation provide immunity for the pharmacists making the substitution in compliance with state laws

Addressing Interchangeability

- In Florida, **Fla. Stat. §465.0252** shows no explicit language stating that the pharmacist MUST NOTIFY the prescriber per se
  - Pharmacists are only able to conduct automatic substitution if the prescriber does not express a preference against substitution in writing, verbally, or electronically.
- Controversy of the status of “interchangeability”
  - ASCO recently published a policy statement advising that Congress should pass legislature amending the BPCIA act to remove the term as it is unnecessary and creates barriers & confusion

Addressing Formulary Management – Single Use

Drug Information

- Review of historical use of reference product
- Identify affected ordering tools (EHR team)

Purchasing

- Product availability
- Communicate estimated use to wholesaler

Drug Information

- Convene stakeholders to develop plan
- Update resources, charts, and references if applicable

Griffith N et al. Hosp Pharm. 2014;49(9):813-25 Villanueva MN et al. Am J Health-Syst Pharm. 2021;78:249-60

Addressing Formulary Management – Single Use

EHR Team

- **Configure medication record**

Purchasing

- **Drug procurement**

EXCUTION

Follow-up Education & Monitoring

- **Provide education and monitor for nonformulary use, if applicable**

Addressing Formulary Management – Additions

Drug Information

- **Deeper dive into drug info, paying close attention to clinical evidence, financial impact and number of patients on reference biologic's PAP**

P&T Committee

- **Formulary review and final deliberation on feasibility of biosimilar addition**

Pharmacy Administration

- **Inventory management, exploration of pricing opportunities and creating a go-live date based on timeline and IT logistics**

Addressing Formulary Management – Additions

IRB

- **Update clinical research protocols that focus on the reference biologic, and add new biosimilar(s) to record via protocol amendments**

EHR Team

- **Configure biosimilar EHR order integration (if not done already) and ensure electronic prior authorization process is connected**

Clinical Pharmacy Specialists

- **Pharmacy to validate biosimilar medication record interchanges in treatment plans**

Addressing Formulary Management – Additions

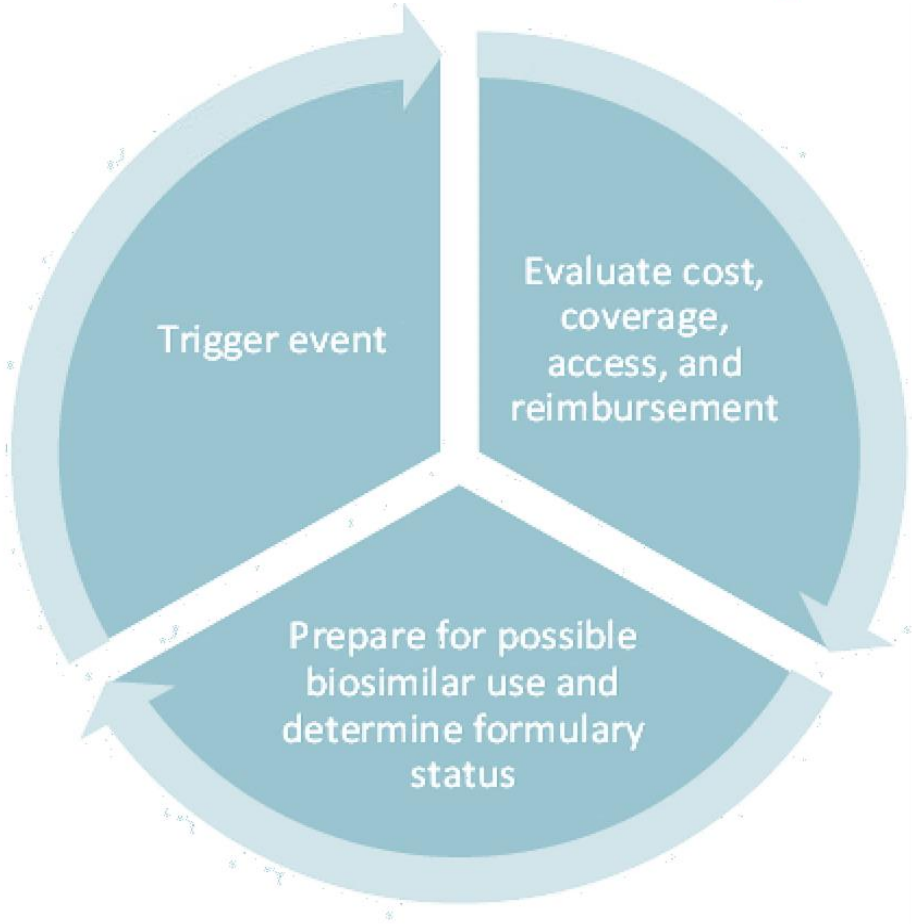
GO LIVE & Follow-Up

- **Initiate go live and communicate and collaborate with team to ensure seamless transition process. Once reference biologic depleted and transition complete, follow processes for formulary deletion of reference product (if applicable)**

Integrating Biosimilars into Practice

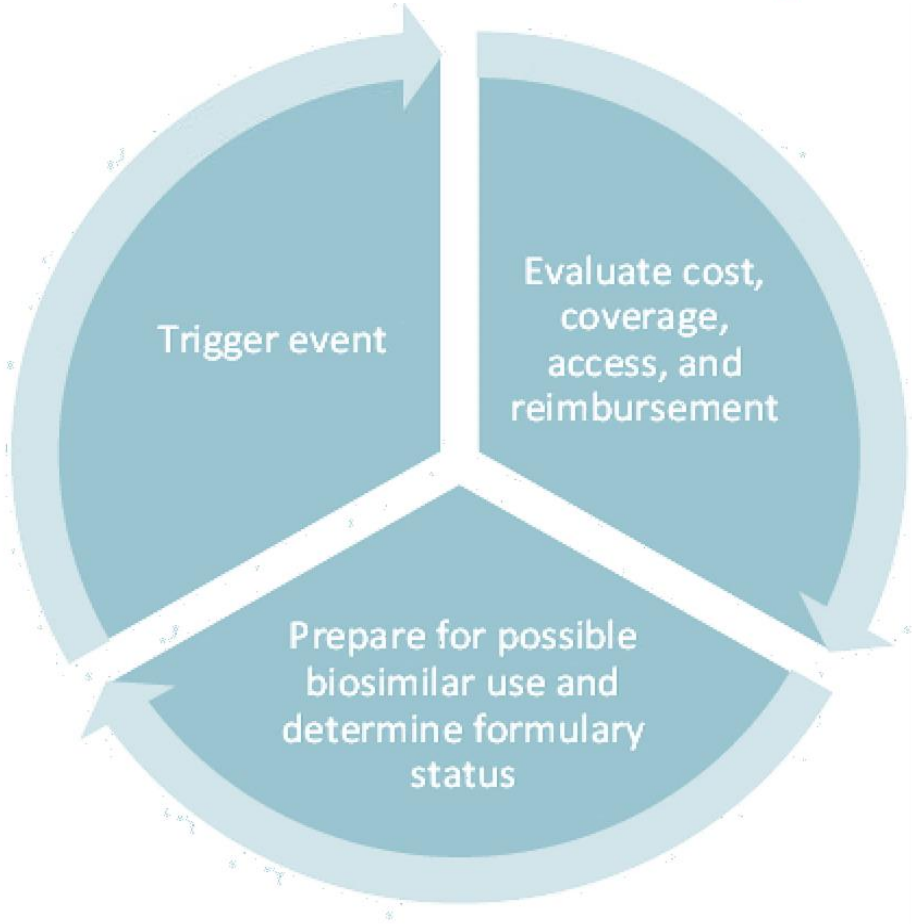
Creating a Program – MD Anderson Example

- **Trigger Event Examples**
  - New Product launch
  - Formulary addition request submission
  - Payer notice or bulletin regarding policy change
  - Notification from a payer during prior authorization that a biosimilar is required



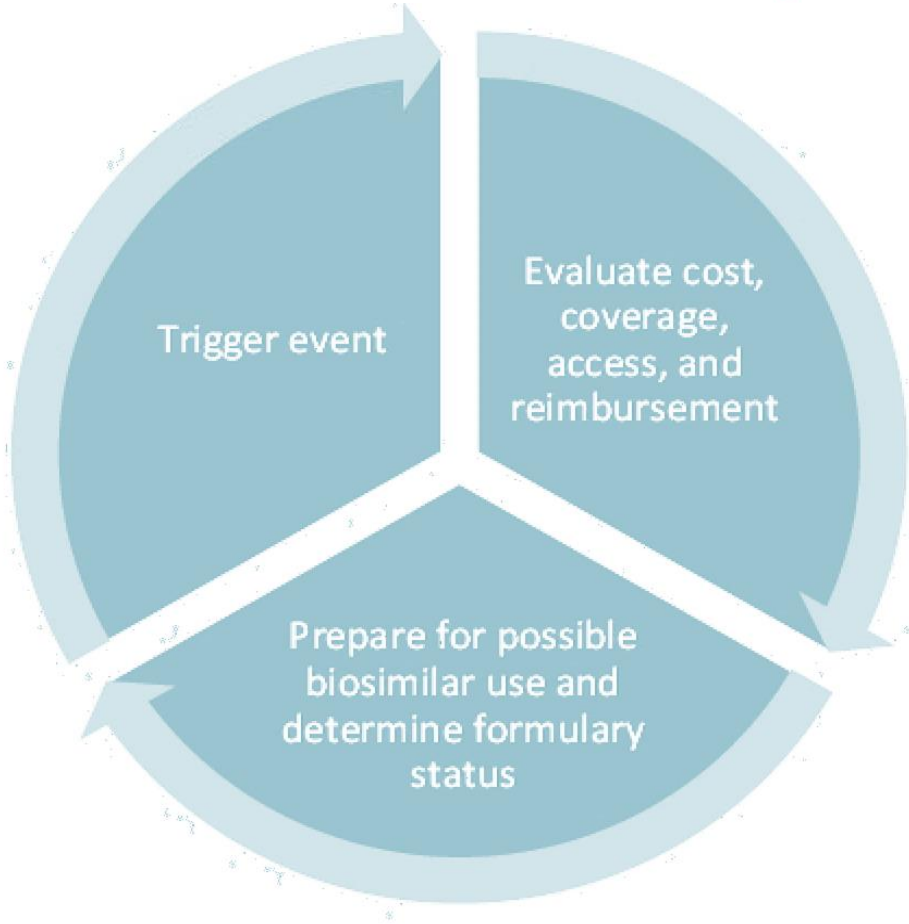
Creating a Program – MD Anderson Example

- **Evaluation of cost, coverage, access and reimbursement**
  - Evaluate federal and commercial payer policies, ease of access, reimbursement support, and cost differences
  - Is biosimilar required by payer?
  - What is process for off-label uses?
  - Patient access programs for both the biosimilar(s) and reference product?



Creating a Program – MD Anderson Example

- **Prepare for Biosimilar use and perform formulary assessment**
  - Formulary addition may be necessary if biosimilar required by payers → the appropriate channels should be consulted (requesting physician, P&T committee, inventory specialist(s), etc.)
  - For institutions with inpatient and outpatient settings, formulary addition may be dichotomous



Closing Remarks

- Biosimilars shown equivalent safety and effectiveness to their reference products with the ability to lower healthcare costs
- Some barriers are systematic and require varying stakeholders for rectification, but provider education is a barrier that can be addressed relatively easily via the clinical team
- Once education is optimal, the next level of biosimilar adoption can take place to further cost-savings & access to care

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Questions & Discussion