THE BASICS OF BIOSIMILARS: UNDERSTANDING THEIR PLACE IN THERAPY

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DISCLOSURE

There are no financial or professional conflicts of interest to disclose.

The views provided in this presentation are my own and do not reflect that of AKPhA or The Alaska Native Tribal Health Consortium.

OBJECTIVES

Pharmacist

- Describe the biosimilar approval process.
- Compare and contrast the interchangeability of a biosimilar agent with the parent biologic based on current FDA labeling.
- Demonstrate how to implement the addition of a biosimilar agent to a hospital formulary.
- Outline a treatment regimen for an eligible patient to switch from a parent biologic to the biosimilar agent.

Technician

- Recognize the brand and generic names of biosimilar agents available on the US market.
- Explain the differences between a parent biologic and its biosimilar agent.
- Identify the benefits and drawbacks of adding biosimilar agents to an institutions formulary.

BIOLOGICS PRICE COMPETITION AND INNOVATION ACT[1]

- **March 2010**: creation of an abbreviated approval pathway for a biosimilar product release, with or without interchangeability with the FDA-approved reference product.

- Conceptually similar to the Drug Price Competition and Patent Term Restoration Act of 1984.

- Use of this abbreviated pathway would allow for decreased costs in bringing drugs to market (specifically biologic drugs) which would allow for savings to be passed on to patients and medical institutions.

BASIC TERMINOLOGY[2]

- **Biologic medications**: large proteins made from living organisms or microorganisms that are naturally heterogeneous in their amino acid composition

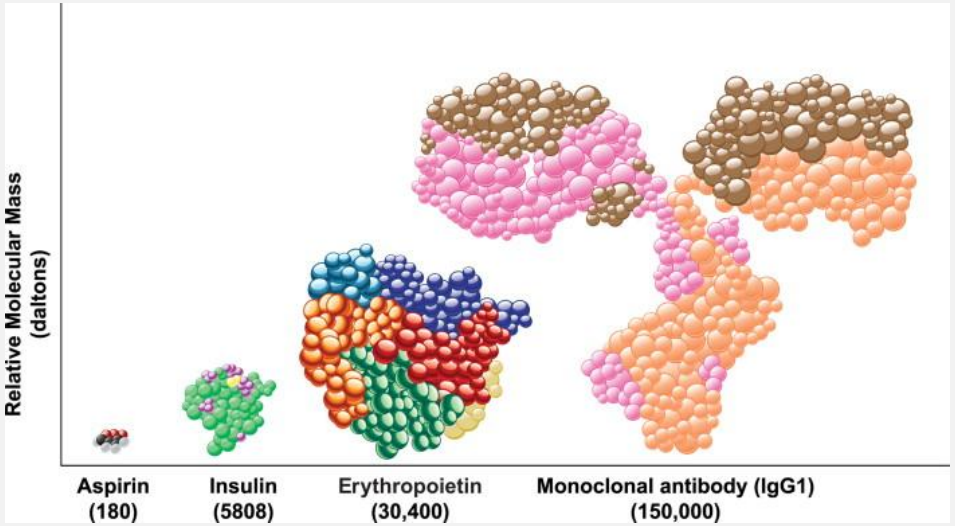
- **Reference products**: a biologic medication in which biosimilar medications are compared to ensure there are no clinically meaningful differences between the two.
  - Ex: reference product is Remicade® (infliximab); biosimilar product is Renflexis® (infliximab-abda)

BASIC TERMINOLOGY[2,3]

- **Biosimilar medications**: biological medications that are highly similar to and that has no clinically meaningful differences compared to the reference product.

- **"Highly similar"** → analysis of the structure and function of the biosimilar vs. reference product
    - Testing purity, potency, chemical identity, and bioactivity

- **"No clinically meaningful differences"** → the manufacturer must demonstrate that the biosimilar medication has no clinically meaningful differences in terms of safety and efficacy through pharmacokinetic and pharmacodynamics studies.



QUESTION

- Prior to FDA approval, the clinical data that brings a biosimilar to market must demonstrate what?
  A. Safety and efficacy data for all FDA approved indications carried by the reference product
  B. Safety and efficacy data for at least one FDA approved indication carried by the reference product
  C. No safety or efficacy data is needed, animal studies and toxicology studies are sufficient in the study of biosimilars

APPROVAL PROCESS[4]

- General requirements:
  - The biosimilar product must have the same mechanism of action as the reference product.
  - Indications for the biosimilar product have been studied and approved by the FDA in the reference product.
  - Route of administration, dosage form, and strength of the biosimilar product are the same as the reference product.
  - The facility in which the drug is manufactured meets current good manufacturing practice regulations.

Preclinical/animal models

- Focus on structure and function
- Safety and/or toxicity

Phase I + II: Clinical pharmacology

- Immunogenicity
- Pharmacokinetics, pharmacodynamics

Phase III: Additional clinical studies

- May be included to provide data compared to the reference product in a specific disease state

WHERE DO BIOSIMILARS FIT INTO CLINICAL PRACTICE?

Interchangeability and indications

QUESTION

- **True or false**: the term "interchangeable" is synonymous with "biosimilar", and all biosimilars may be used interchangeably with the reference product.

INTERCHANGEABILITY[4]

Switching between the reference product and biosimilar product → No increase in safety risks or decrease in clinical efficacy.

Clinical data must demonstrate that the biosimilar product will produce the same clinical response in **any given patient.**

Interchangeable products may be substituted for the reference product without consultation with the prescriber.

INTERCHANGEABILITY[4]

CURRENTLY THERE ARE NO BIOSIMILARS ON THE MARKET THAT ARE DEEMED INTERCHANGEBALE

decrease in clinical efficacy.

any given patient.

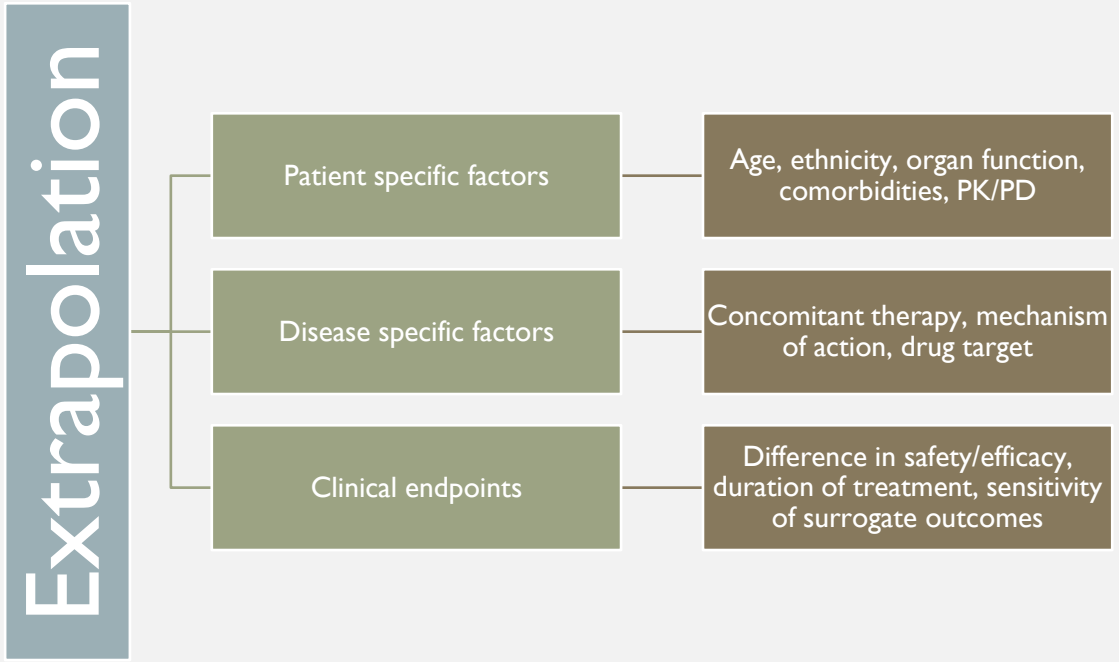
consultation with the prescriber.

INTERCHANGEABILITY

- The term “interchangeable” does not limit a facility’s use of the biosimilar.
- This term is regulatory in nature and limit’s the pharmacist’s ability to use the biosimilar interchangeably with the biologic without consultation with the provider.
- If a biosimilar product is not deemed as interchangeable it does not inhibit the facility’s ability to create protocols to use the biosimilar product in place of the biologic product.

FDA APPROVED INDICATIONS[4]

- A biosimilar product may be approved for an indication in which there are no direct clinical studies.
- This extrapolation of data is not an assumption – rather, it is scientifically justified based on the information known regarding the biosimilar product, reference product, and overall safety/efficacy data.



CURRENT BIOSIMILAR APPROVALS

Biosimilar Name	Reference Product	Approval Date
Mvasi (Bevacizumab-awwb)	Avastin (bevacizumab)	September 2017
Zirabev (bevacizumab-bvzr)	Avastin (bevacizumab)	June 2019
Erelzi (Etanercept-szzs)	Enbrel (etanercept)	August 2016*
Eticovo (etanercept-ykro)	Enbrel (etanercept)	April 2019*
Retacrit (epoetin alfa-epbx)	Epogen (epoetin-alfa)	May 2018
Herzuma (trastuzumab-pkrb)	Herceptin (trastuzumab)	December 2018
Kanjinti (trastuzumab-anns)	Herceptin (trastuzumab)	June 2019
Ogivri (trastuzumab-dkst)	Herceptin (trastuzumab)	December 2017
Ontruzant (trastuzumab-dttb)	Herceptin (trastuzumab)	January 2019
Trazimera (trastuzumab-qyyp)	Herceptin (trastuzumab)	March 2019
Abrilada (adalimumab-afzb)	Humira (adalimumab)	November 2019*
Amjevita (Adalimumab -atto)	Humira (adalimumab)	September 2016*
Cyltezo (Adalimumab-adbm)	Humira (adalimumab)	August 2017*
Hadlima (adalimumab-bwwd)	Humira (adalimumab)	July 2019*
Hulio (adalimumab-fkjp)	Humira (adalimumab)	July 2020*

Biosimilar Name	Reference Product	Approval Date
Hyrimoz (adalimumab-adaz)	Humira (adalimumab)	October 2018*
Fulphila (pegfilgrastim-jmdb)	Neluasta (pegfilgrastim)	June 2018
Nyvepria (pegfilgrastim-apgf)	Neulasta (pegfilgrastim)	June 2020
Udenyca (pegfilgrastim-cbqv)	Neulasta (pegfilgrastim)	November 2018
Ziextenzo (pegfilgrastim-bmez)	Neulasta (pegfilgrastim)	November 2019
Nivestym (filgrastim-aafi)	Neupogen (filgrastim)	July 2018
Zarxio (Filgrastim-sndz)	Neupogen (filgrastim)	March 2015
Avsola (infliximab-axxq)	Remicade (infliximab)	December 2019
Inflectra (Infliximab-dyyb)	Remicade (infliximab)	April 2016
Ixifi (infliximab-qbtx)	Remicade (infliximab)	December 2017*
Renflexis (Infliximab-abda)	Remicade (infliximab)	May 2017
Riabni (rituximab-arrx)	Rituxan (rituximab)	December 2020
Ruxience (rituximab-pvvr)	Rituxan (rituximab)	July 2019
Truxima (rituximab-abbs)	Rituxan (rituximab)	November 2018

*not currently available for purchase in the US

MAKING THE SWITCH

What patients are eligible? Is it worth switching? How do we implement this change?

QUESTION

- A provider asks you, the pharmacist, about a newly approved biosimilar medication for the treatment of rheumatoid arthritis. They want to know if it would be worth adding to the hospital formulary, what must you first consider?
  A. Patient population and expected use
  B. Robustness of clinical data showing safety/efficacy
  C. Reimbursement from third-party payers
  D. All of the above

CONSIDERATIONS

Biosimilar products may not carry the same indications as the reference product OR may have limited data to support use in certain clinical conditions outside of extrapolation

Use of a biosimilar could result in a large cost savings to both the institution and the patient

Possible differences in efficacy, adverse reactions, immunogenicity

Opportunity for collaborative care in providing information about biosimilars

Increased access to care for the patient

Hesitancy from prescribers

Differences in preparation of the new product

INTERDISCIPLINARY CARE DECISIONS

- Collaboration with prescribers, pharmacy and therapeutics committees, and pharmacy management is necessary prior to the implementation of biosimilar products.

- It is imperative that pharmacists and providers work together to determine what is best for the patient (and the institution).
  - Risks vs. benefits – consider both therapeutic and financial impacts.

- Address concerns and hesitancy from providers – what are the major reasons causing this hesitancy?

PROVIDER HESITANCY[1,2]

REASON FOR HESITANCY

1. Concern for immunogenicity
2. Perception of inadequate clinical data (safety and efficacy)
3. Patient perception – patient may not accept the switch or "nocebo" effect

SUPPORTIVE ACTION

1. Provide clinical data – neutralizing antibodies, anti-drug antibodies, adverse effect rates, etc.
2. Provide education – discuss "abbreviated" approval process, indication extrapolation, look for additional medical literature
3. Create educational handouts or provide pharmacist consultation– involve them in the discussion if appropriate

ALASKA NATIVE MEDICAL CENTER (ANMC)

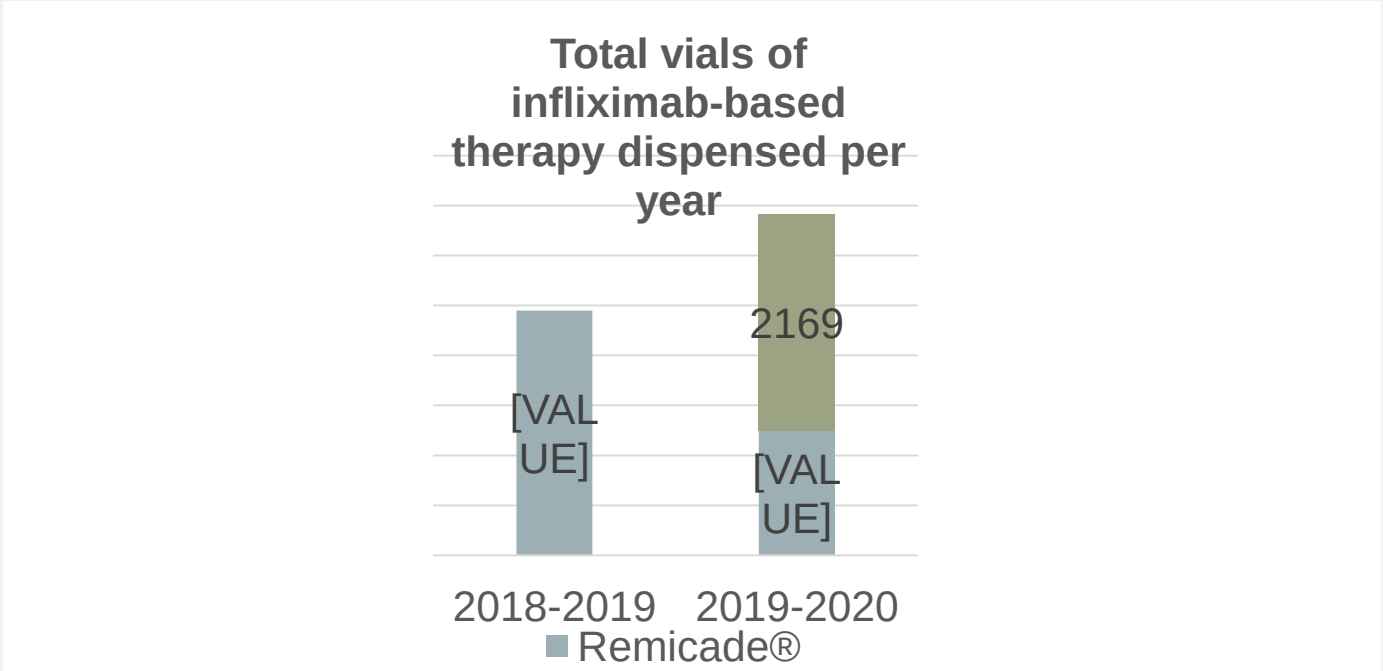
October 2019 – ANMC Pharmacy and Therapeutics Committee

Addition of Renflexis® (infliximab-abda) to the formulary.

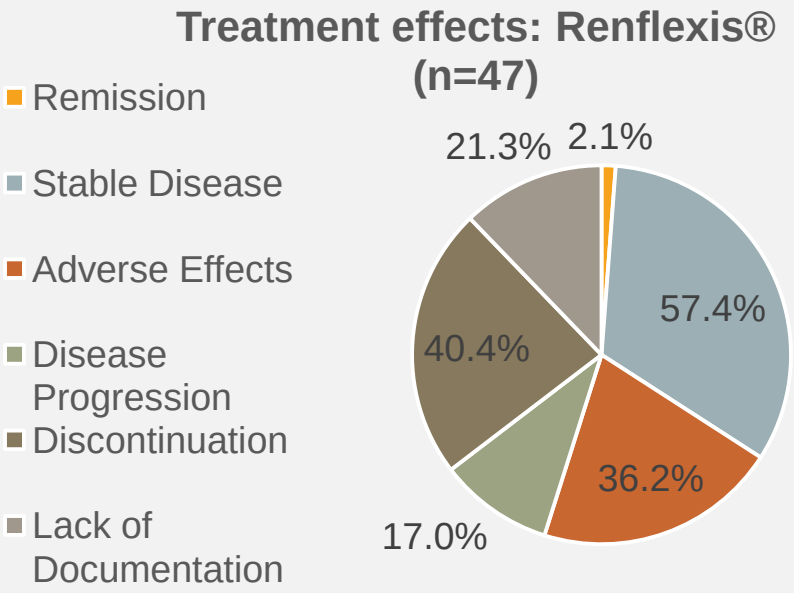
- Renflexis® is currently being used in place of Remicade® for most patients.
- This substitution is being applied in most patients if deemed appropriate by their physicians' clinical judgement; however, there is not an automatic substitution protocol in place for this change to be initiated by pharmacy.
- What were we looking for?
  - Financial impact
  - Therapeutic equivalence

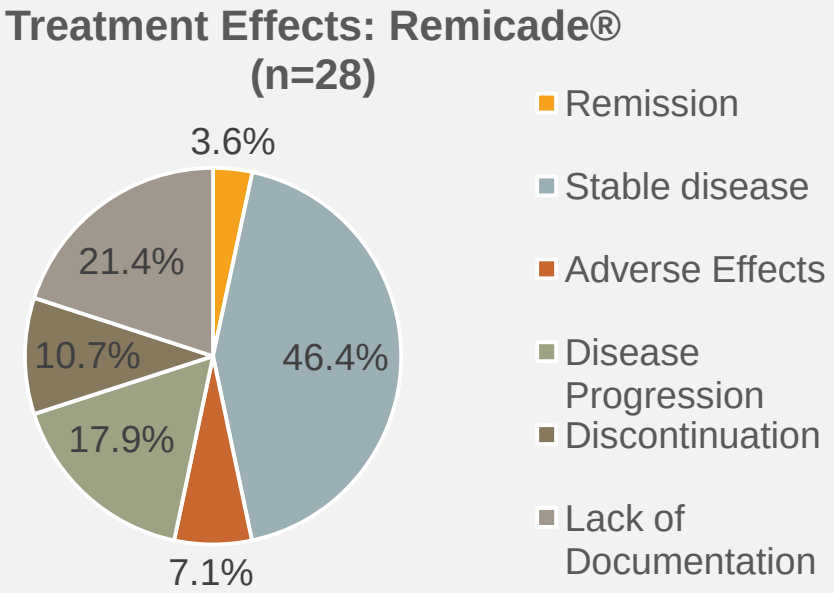
UTILIZATION

- Comparing the drug utilization reports from 2018-2019 and 2019-2020, there was an increase of 28.2% in the use of infliximab-based therapy.
- The results of this review indicate a savings of $500,039.84 associated with the switch to Renflexis® from Remicade®. Nearly two-times as many vials of Renflexis® were purchased compared to Remicade® but due to the lower cost of Renflexis ®, pharmacy was able to spend less.



Year	Pharmacy Expenditure Remicade® + Renflexis®
2018-2019	$1,386,040.50
2019-2020	$886,000.66





TREATMENT EFFECTS

- Clinical remission achieved in 2.1% vs. 3.6% of patients in the Renflexis® and Remicade® groups respectively.
- There were more patients that were documented to have stable disease in the Renflexis® group compared to Remicade®.
- There were more treatment failures in the Renflexis® group compared to Remicade®.

TREATMENT DISCONTINUATION[8,9,10,11]

- Drug-induced lupus erythematosus, infusion reactions, CNS demyelination, and loss of efficacy are well documented class effects of TNF-alpha inhibitors.
- The occurrence of these effects cannot be directly attributed to the use of the biosimilar.

Reasons for Discontinuation of Renflexis® and Remicade®		
	Renflexis®, n (%) (n=17)	Remicade®, n (%) (n=3)
Drug-induced systemic lupus erythematosus	2 (10.5%)	0
Infusion reactions	5 (26.3%)	2 (66.7%)
Lack of efficacy	5 (26.3%)	1 (33.3%)
Demyelinating lesions of the thoracic spine	1 (5.3%)	0
COVID-19 travel concerns	4 (21.1%)	0

REMICADE® VS. RENFLEXIS®[6]

- Big picture:
  - Increased utilization from 2019-2020 still allowed for ~$500,000 savings in drug procurement costs.
  - An equivalent proportion of patients were able to achieve stable disease between the two drugs.
  - Disease progression rates between the two groups were proportional.
  - Adverse effects seen with Renflexis® were not specific to the drug itself – rather, they have been widely documented as class effects.

GENERAL APPROACH

Patient

- Who are treating? → holistic patient approach
- What are we treating? → FDA labeled indications, clinical data

Institution

- Pharmacy logistics → stability, preparation, ordering
- Cost of procurement
- Reimbursement rates based on the patient population and insurance
- Pharmacovigilance

Collaboration

- Presentation of the above data to the necessary committees and providers
- Education materials for patients, providers, and other members of the healthcare team
- Provider and pharmacist collaboration in monitoring safety and efficacy

WANT MORE GUIDANCE? LOOK TO INTERNATIONALLY[12]

- The European Medicines Agency (EMA) has taken large steps in implementing biosimilars into their medical practices.
  - Medical societies throughout Europe have published recommendations for utilizing biosimilars over the biologic reference product at the provider level.
- Denmark's nationwide adoption of Inflectra® over the reference product, Remicade®
- Task Force on the Use of Biosimilars to Treat Rheumatological Diseases is in agreement that the use of biosimilars is supported by adequate clinical evidence in inflammatory immune diseases
  - Made up of multidisciplinary physicians, pharmacologists, and patient representatives from the US, Japan, and 8 European countries

QUESTION

- **Let's revisit this question, but this time walk yourself through the general approach you would take in a real life situation based off the general approach discussed in this activity.**
- A provider asks you, the pharmacist, about a newly approved biosimilar medication for the treatment of rheumatoid arthritis. They want to know if it would be worth adding to the hospital formulary, what must you first consider?

BARRIERS AND CONSIDERATIONS

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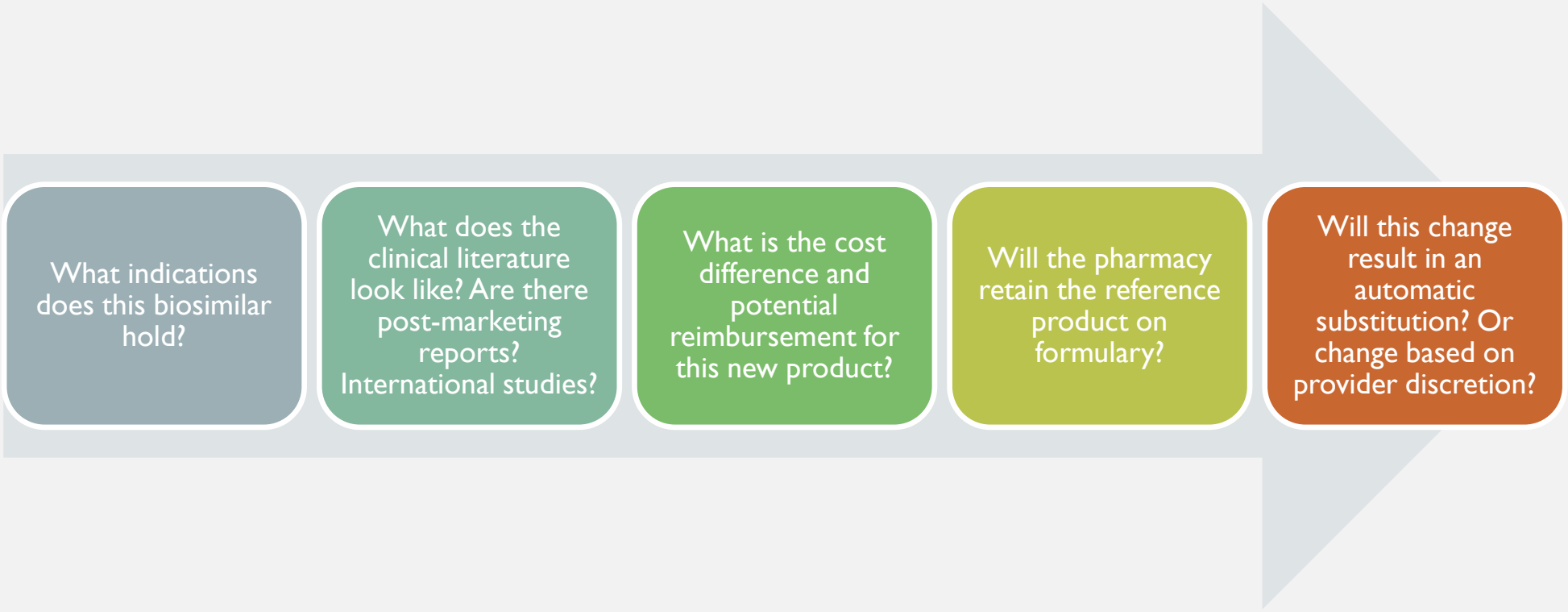
What is the cost difference and potential reimbursement for this new product?

BARRIERS AND CONSIDERATIONS

- What indications does this biosimilar hold?
- What does the clinical literature look like? Are there post-marketing reports? International studies?
- What is the cost difference and potential reimbursement for this new product?
- Will the pharmacy retain the reference product on formulary?

BARRIERS AND CONSIDERATIONS



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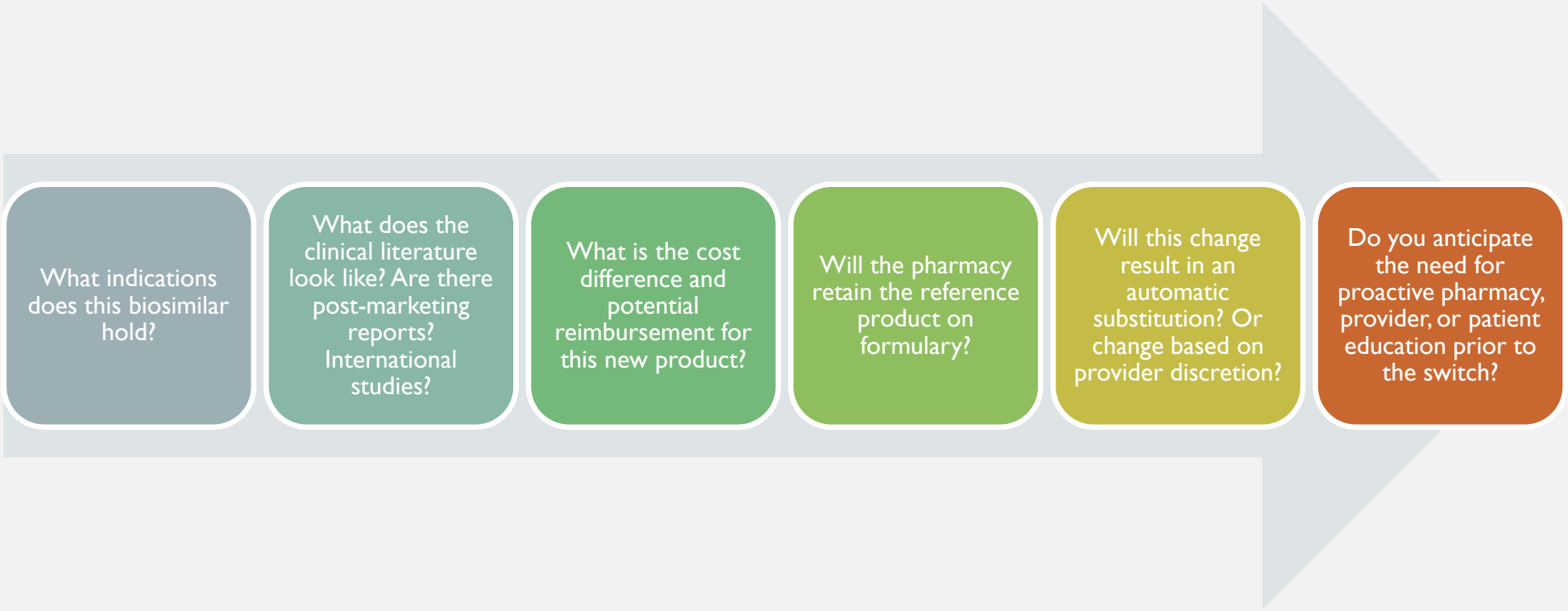

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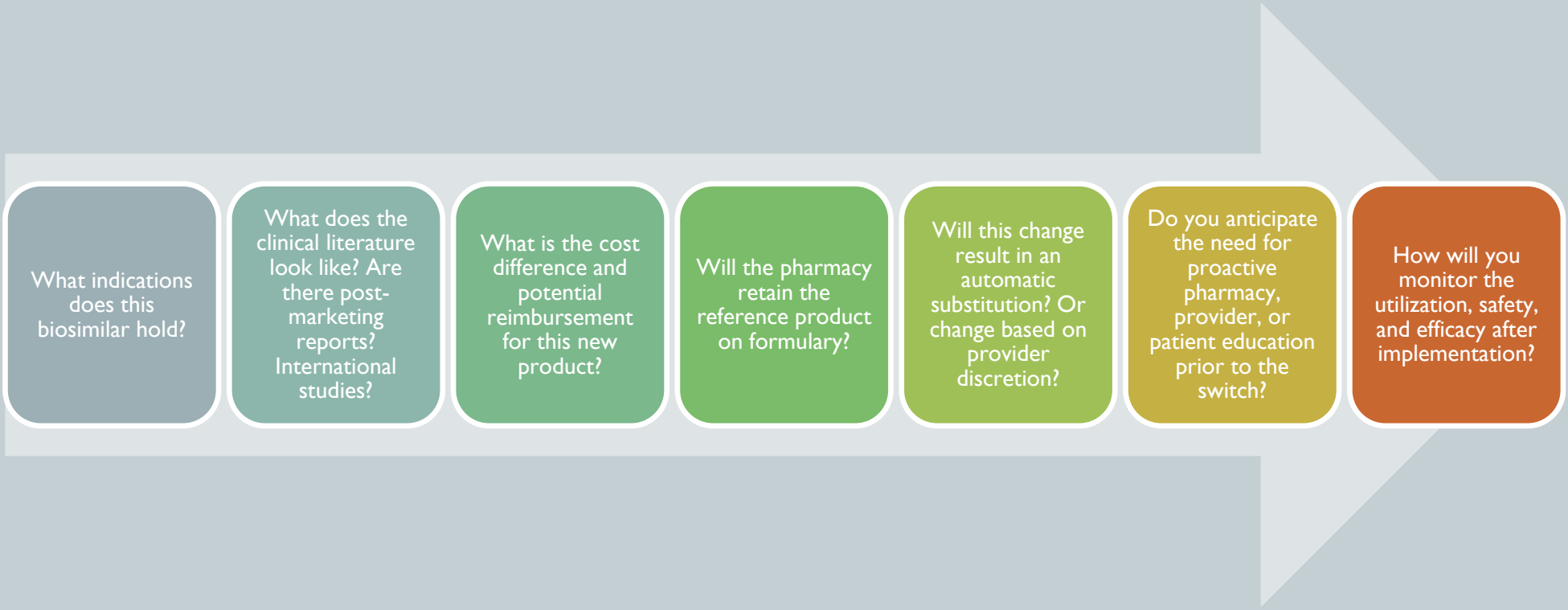

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