Clinical, financial, and practical considerations for biosimilar use at an Alaska Native Hospital

Jessica Hiney, PharmD – PGY1 Pharmacy Practice Resident

Co-authors: Adam C Harris PharmD, BCPS, CPHQ, CCMSCP, Kara King PharmD, MPH, NCPS, David Moore PharmD, BCPS

Alaska Native Tribal Health Consortium

IRB Exempt

Disclosure Statement

I, Jessica Hiney, have no personal, professional, or financial conflicts of interest to disclose.

The information presented is subject to differing interpretations, is educational in nature, and abides by the non-commercial guidelines.

Objectives

- Develop an institutional methodology for the implementation of biosimilars to a hospital formulary.
- Identify the obstacles in biosimilar formulary management when creating a monograph.

Alaska Native Tribal Health Consortium

The Alaska Native Medical Center (ANMC) operates a state-of-the-art, 173-bed hospital providing comprehensive medical services to Alaska Native and American Indian people. ANMC was Alaska's first Level II Trauma Center, is a Level II Pediatric Trauma Center and a Comprehensive Pediatric Emergency Center.

ANMC also provides specialty care services including hematology/oncology, endocrinology, cardiology, nephrology, and more.

Mission statement: Providing the highest quality health services in partnership with our people and the Alaska Tribal Health System.

Pre-Test Assessment

1. Which of the following is the most important consideration to evaluate prior to monograph creation?
   a) Provider/patient acceptance of the change
   b) Supply chain management and medication shortages
   c) Differences in vial size availability compared to the reference product
   d) FDA approval of a biosimilar as “interchangeable”
2. Practical and operational details should be considered throughout monograph creation and P&T consideration. What is an example of an operational detail?
   a) Literature searches for post marketing safety surveillance
   b) Managing the biosimilar and reference product within the pharmacy
   c) Extrapolated indication comparisons
3. Which of the following are categories that should be highlighted within a biosimilar monograph? (Select all that apply)
   a) Pharmacokinetic and pharmacodynamic data comparisons
   b) Clinical efficacy endpoint comparisons
   c) Extrapolated indications
   d) Post marketing safety surveillance
   e) Internal pharmacovigilance (safety monitoring) reports

Background

Basic terminology, biosimilar production pathway, interchangeability, FDA approved indications

A star indicates information that should be included in the biosimilar monograph template

Biologics Price Competition and Innovation Act[1,2,15,16]

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[2,3,15,16]

- **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 showing there are no clinically meaningful differences between the two.

  Ex: reference product is Remicade® (infliximab); biosimilar product is Renflexis® (infliximab-abda)
- **Biosimilar medications**: biological medications that are highly similar to and that has no clinically meaningful differences compared to the reference product.

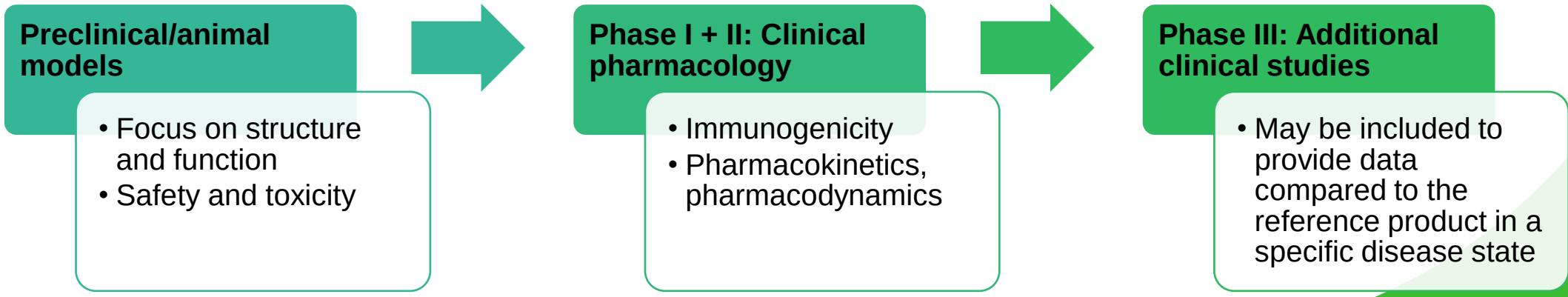
- **"Highly similar"** → analysis of the structure and function of the biosimilar vs. reference product

  Testing purity, potency, chemical identify, and bioactivity in animals and humans

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

Approval Process and Clinical Studies[4,15,16]

- 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.**



Clinical Considerations

Safety, efficacy, structure of clinical studies, extrapolated indications

Clinical Literature[14-16]

Human PK/PD Data

- Generally considered essential to designate biosimilarity.
- Comparable PK/PD data to reference product will likely support biosimilarity.
- Established PK/PD data in combination with a favorable immunogenicity profile could provide enough evidence to show there is no clinically meaningful difference between products.

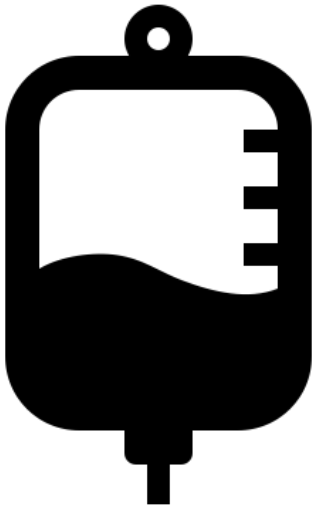
Immunogenicity

- Increased immunogenicity reactions can affect both safety and efficacy.
  - Anaphylactoid reactions
  - Development of neutralizing antibodies → loss of clinical response.
- Recommended to assess immunogenicity in all human studies.
- Ensure that clinical follow up to evaluate potential delayed immune responses are appropriate in studies.

Clinical Literature[1,2,4,5,14-16]

COMPARATIVE CLINICAL EFFICACY

- Clinical endpoints used in phase III studies should be relevant to the disease state.
  - ***Remember – may not be the best indicator of clinical similarity as these endpoints are likely less sensitive in determining a difference***
- Refer back to the studies for the reference product to compare patient characteristics.
  - **There are instances where it may be appropriate to have differences in inclusion criteria.**
- Duration of the study should be long enough to meaningfully determine clinical efficacy as well as delayed immunogenic responses.



The following requirements must be met in order for a biosimilar product to be designated as interchangeable with the reference product, per the FDA.

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[1,2,4,5,14-16]

The following requirements must be met in order for a biosimilar product to be designated as interchangeable with the reference product, per the FDA.

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

increase in safety risks or decrease in clinical efficacy.

produce the same clinical response in **any given patient**.

consultation with the prescriber.

Interchangeability[1,2,4,5,14-16]

Interchangeability[1,2,4,5,14-16]

The term “interchangeable” does not limit a facility’s use of the biosimilar.

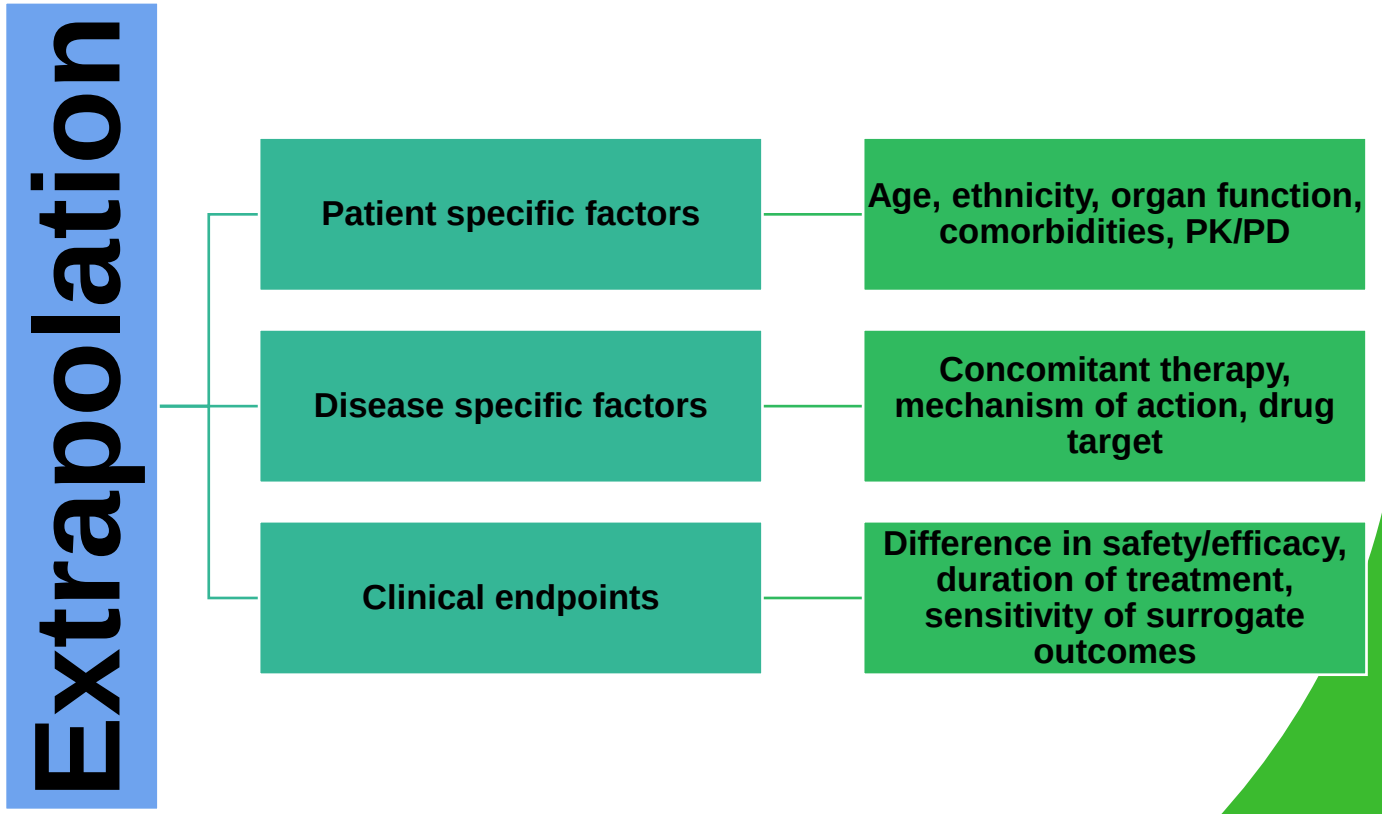
This term is regulatory in nature and limits the pharmacist’s ability to use the biosimilar interchangeably with the biologic without consultation with the provider.

If a biosimilar product is not deemed as interchangeable by the FDA, it does not inhibit the facility’s ability to create protocols to use the biosimilar product in place of the biologic.

FDA approved indications[1,2,4,5,14-16]

- 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.



Practical Considerations

Cost of procurement, pharmacovigilance, patient and provider hesitancy and education, reimbursement, P&T considerations

Supply Chain Management[1-3,11]

- A consideration to investigate prior to monograph creation includes the reliability of the manufacturer in maintaining adequate drug supply.

- Considerations:

  Does the manufacturer have a history of drug shortage?

  Does the manufacturer have a contingency plan for management of shortages?

  Do facilities have a history of compliance with good manufacturing practices?

Pharmacovigilance[8-11]

- Should be well thought out prior to implementation of the biosimilar to formulary.
- Internal reporting of adverse effects:

  Expected adverse effects (i.e. drug class effects) vs. immunogenic responses.

  Considerations:

  How often will this data be analyzed and reported to management?

  How will sound-alike look-alike drug (SALAD) issues be handled?

  How will safety guards and comments be built into the EHR to ensure correct ordering?

Total Cost[1,2,15,16]

- Includes the direct cost of the drug as well as the indirect costs that come along with handling and monitoring.

Direct cost considerations:

Differences in unit sizes (ex: 5mL vs. 10mL)

Differences in # of units per orderable package

Differences in cost per available premade dose

Indirect cost considerations:

Pharmacovigilance

Prior authorization management

Time spent training staff on differences between drugs (storage, preparation, handling)

Building order sets in the electronic health record

Insurance Reimbursement

In health systems that maintain both inpatient and outpatient-based pharmacies, a major consideration with any drug use is anticipated reimbursement.

Our institution relies on internally derived calculations to determine anticipated reimbursement based on the ratio of privately/publicly insured patients.

Interdisciplinary Care Decisions[13,14]

- 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 <u>therapeutic</u> and <u>financial impacts</u>

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

Provider and Patient Perspectives[13,14]

- The American Society of Clinical Oncology – biosimilar position statement (2018)

  Essential topic for evaluation prior to use of biosimilars in practice:

  1. **Naming of drug**
  2. **Labeling (FDA approved indications)**
  3. **Interchangeability**
  4. **Switching**
  5. **Substitution**

- In a patient derived survey from 2016, 6% of patients were informed on the presence of biosimilars on the U.S. market.

  Keeping patients informed and educated about a switch to a biosimilar is of the utmost importance

Hesitancy[13]

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 if available
3. Create educational handouts or provide pharmacist consultation– involve them in the discussion if appropriate.

Conclusions

- Although it is not necessarily desirable to continuously highlight differences between the reference product and biosimilar product, because in theory these medications will ideally be interchangeable, it is necessary to compare relevant differences in order to make sure the drug is used safely and effectively.

- Rationale behind completing biosimilarity studies is not to re-establish the drug's clinical efficacy, rather, to infer clinical efficacy through establishment of biosmilarity.

- Developing an eye for the pertinent information necessary to highlight in biosimilar monograph completion is essential to safely and effectively implementing new drugs.

Biosimilar Monograph Highlights

Clinical information	Indications	Post marketing surveillance data	Differences in handling	Pharmacovigilance
Pharmacokinetics Pharmacodynamics Clinical efficacy endpoints	Extrapolated vs. Studied	Include if available Prioritize information published from third parties.	Compounding # of units in orderable package	Plan for further P&T follow up Internal AE reporting Naming - SALAD

Post-Test Assessment

1. Which of the following is the most important consideration to evaluate prior to monograph creation?
   - **a) Provider/patient acceptance of the change**
   - b) Supply chain management and medication shortages
   - c) Differences in vial size availability compared to the reference product
   - d) FDA approval of a biosimilar as “interchangeable”
2. Practical and operational details should be considered throughout monograph creation and P&T consideration. What is an example of an operational detail?
   - a) Literature searches for post marketing safety surveillance
   - **b) Managing the biosimilar and reference product within the pharmacy**
   - c) Extrapolated indication comparisons
3. Which of the following are categories that should be highlighted within a biosimilar monograph? (Select all that apply)
   - a) Pharmacokinetic and pharmacodynamic data comparisons
   - b) Clinical efficacy endpoint comparisons
   - c) Extrapolated indications
   - d) Post marketing safety surveillance
   - e) Internal pharmacovigilance (safety monitoring) reports

References

1. Cuellar S, McBride A, Medina P. Pharmacist perspectives and considerations for implementation of therapeutic oncology biosimilars in practice. *Am J Health Syst Pharm*. 2019;76(21):1725-1738.
2. Stevenson JG, Popovian R, Jacobs I, Hurst S, Shane LG. Biosimilars: practical considerations for pharmacists. *Ann Pharmacother*. 2017;51(7):590-602.
3. Lammers P, Criscitiello C, Curigliano G, Jacobs I. Barriers to the use of trastuzumab for her2+ breast cancer and the potential impact of biosimilars: a physician survey in the united states and emerging markets. *Pharmaceuticals (Basel)*. 2014;7(9):943-953.
4. Ventola CL. Evaluation of biosimilars for formulary inclusion: factors for consideration by p&t committees. *P T*. 2015;40(10):680-689.
5. Lucio SD, Stevenson JG, Hoffman JM. Biosimilars: Implications for health-system pharmacists. *Am J Health Syst Pharm*. 2013;70(22):2004-2017.
6. Leber MB. Optimizing use and addressing challenges to uptake of biosimilars. *Am J Manag Care*. 2018;24(21 Suppl):S457-S461.
7. Cohen H, Beydoun D, Chien D, et al. Awareness, knowledge, and perceptions of biosimilars among specialty physicians. *Adv Ther*. 2016;33(12):2160-2172.
8. Lyman GH, Balaban E, Diaz M, et al. American society of clinical oncology statement: biosimilars in oncology. *J Clin Oncol*. 2018;36(12):1260-1265.
9. Jacobs I, Singh E, Sewell KL, Al-Sabbagh A, Shane LG. Patient attitudes and understanding about biosimilars: an international cross-sectional survey. *Patient Prefer Adherence*. 2016;10:937-948.
10. Fenna J, Watkins K, Guirguis M. Biosimilar drugs and the hospital formulary: a canadian experience. *Can J Hosp Pharm*. 2019;72(2):145-150.
11. Griffith N, McBride A, Stevenson JG, Green L. Formulary selection criteria for biosimilars: considerations for us health-system pharmacists. *Hosp Pharm*. 2014;49(9):813-825.
12. Villanueva MN, Davis JE, Sobocinski SM. Navigating uncharted waters: Developing a standardized approach for evaluating and implementing biosimilar products at a comprehensive cancer center. *Am J Health Syst Pharm*. 2021;78(3):249-260.
13. Kolbe AR, Kearsley A, Merchant L, et al. Physician understanding and willingness to prescribe biosimilars: findings from a us national survey. *BioDrugs*. Published online April 7, 2021.
14. Zlatkus A, Bixby T, Goyal K. Considerations for the US health-system pharmacist in a world of biosimilars. *Drugs Context*. 2020;9.
15. U.S. Food and Drug Administration. Biosimilar Prdouct Regulatory Review and Approval. https://www.fda.gove/files/drugs/pubslished/Biosimilar-Product-Regulatory-and-Approval.pdf
16. U.S. Food and Drug Administration. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product – Guidance for Industry. April 2015. https://www.fed.gov/media/82647/download