Biosimilar Implementation in Hematology/Oncology

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PHARMACY SYMPOSIUM 2020

Disclosures

- I have no financial relationships to disclose

Learning Objectives

- Explain the clinical and economic impact of biosimilar use in the treatment of hematology/oncology patients
- Discuss logistical considerations for biosimilar implementation in clinical practice
- Describe strategies to overcome challenges related to biosimilar implementation in hematology/oncology

Introduction to Biosimilar Use Hematology/Oncology

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Question 1: To what degree are biosimilars already integrated into your practice site?

A: No biosimilars yet

B: Supportive care biosimilars only

C: A mix of therapeutic and supportive care biosimilars

D: Full conversion

Biosimilar Scenarios: Part I

- CK is a 67 year old male who presents to the oncology clinic for treatment of his malignancy. The physician prescribes chemotherapy which includes Xmab as part of the treatment regimen
- The physician mentions the possible use of biosimilars to the patient as part of the consent process. CK asks if a biosimilar is a generic drug and if it is “as good as” Xmab is for his disease
- Pharmacist is consulted for patient education
- How do you answer the question?

What is a Biosimilar?

- Created by the Biologic Price Competition and Innovation (BPCI) Act of 2009 [abbreviated 351(k) pathway of PHS Act]
- Highly similar to reference products with no meaningful clinical differences to reference (originator) product
- Naming convention contains four letter suffix [applies to all biologics approved after March 2019]
- Not a generic drug

PHS: Public Health Service Act; PK: Pharmacokinetics; PD: Pharmacodynamics
Regulation of Biological Products, 42 USC§262

Biosimilar vs. Generic: Similar Yet Different

- Common goal: decrease drug expenditures while maintaining safety and efficacy of reference product
- Divergence exists on how to achieve that goal:

	Biosimilar	Generic
Production characteristics	Large, complex molecules grown in complex living systems	Small, chemically synthesized molecules
Relationship to reference	• Highly similar • No clinically meaningful differences	Chemically identical
FDA approval pathway	Abbreviated 351(k) pathway	Abbreviated New Drug Application
Substitution guidance	• Purple Book • Manufacturer must apply for extrapolation across indications	• Orange Book • No extrapolation application required
Cost to bring to market	High	Low

J Adv Pract Oncol 2017;8:688–699.

FDA Biosimilar Action Plan Goal: Balance of Competition and Innovation

- FDA Biosimilar Action Plan provides key goals for biosimilar implementation
- The first biosimilar was FDA approved in 2015 which has increased to 28 biosimilar products (and counting)

FDA Biosimilar Action Plan Key Elements
✓ Improve efficiency of biosimilar and interchangeable product development and approval process
✓ Maximize scientific and regulatory clarity for biosimilar development
✓ Develop effective communications to improve understanding of biosimilars among patients, clinicians, payers
✓ Support market competition by reducing attempts to unfairly delay competition

FDA: Food and Drug Administration.

https://www.fda.gov/drugs/biosimilars/biosimilar-product-information. Accessed 8/10/20.
https://www.fda.gov/media/114574/download. Accessed 8/15/20.

FDA-Approved Oncology Biosimilars in 2020

	Reference Product	Biosimilar Products
Supportive Care	Filgrastim (Neupogen®)	• Filgrastim-aafi (Nivestym®) • Filgrastim-sndz (Zarxio®)
	Pegfilgrastim (Neulasta®)	• Pegfilgrastim-apgf (Nyvepria®) • Pegfilgrastim-bmez (Ziextenzo®) • Pegfilgrastim-cbqv (Udenyca®) • Pegfilgrastim-jmdb (Fulphila®)
	Epoetin alfa (Procrit®)	• Epoetin alfa-epbx (Retacrit®)
Therapeutic	Rituximab (Rituxan®)	• Rituximab-abbs (Truxima®) • Rituximab-pvvr (Ruxience®)
	Bevacizumab (Avastin®)	• Bevacizumab-awwb (Mvasi™) • Bevacizumab-bvzr (Zirabev®)
	Trastuzumab (Herceptin®)	• Trastuzumab-anns (Kanjinti™) • Trastuzumab-dkst (Ogivri™) • Trastuzumab-dttb (Ontruzant®) • Trastuzumab-pkrb (Herzuma®) • Trastuzumab-qyyp (Trazimera™)

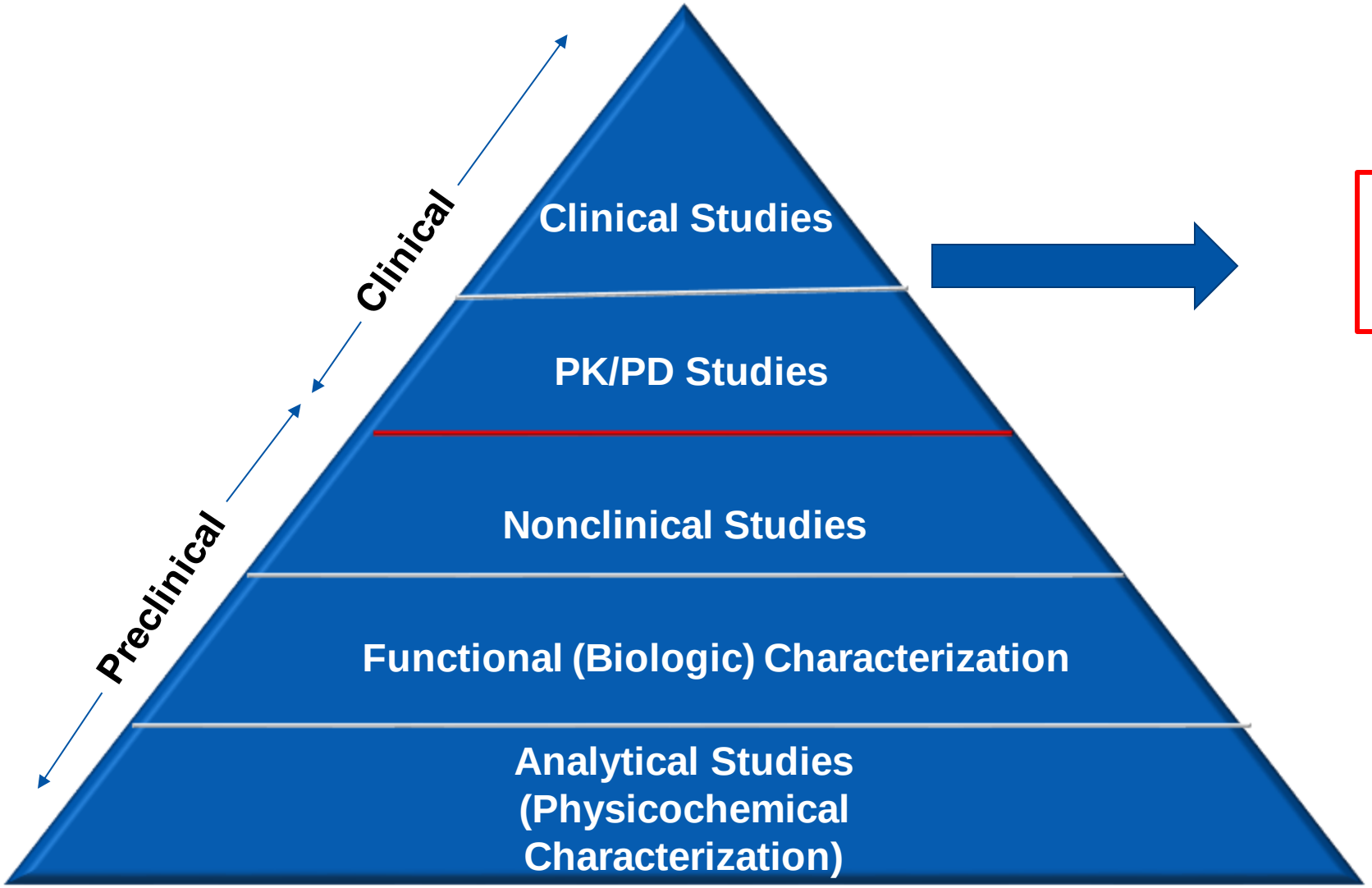
https://www.fda.gov/drugs/biosimilars/biosimilar-product-information Accessed 8/8/20.

Financial Rationale for Biosimilars

- Estimated global market for biologics in 2024: $87 billion (↑ from $56.7 billion in 2018)
  - Over 90% of drugs in oncology development pipeline are biologics
- Biosimilar adoption may decrease US spend on biologics by $54 billion from 2017-2026 (range: $24-150 billion)
  - Estimated 13% cost savings in oncology
  - Variables: industry, regulatory, prescriber, insurer, and policy decisions

Ann Pharmcother 2020;26:1060028020944596.
Rand Health Q.2018;7(4):3.

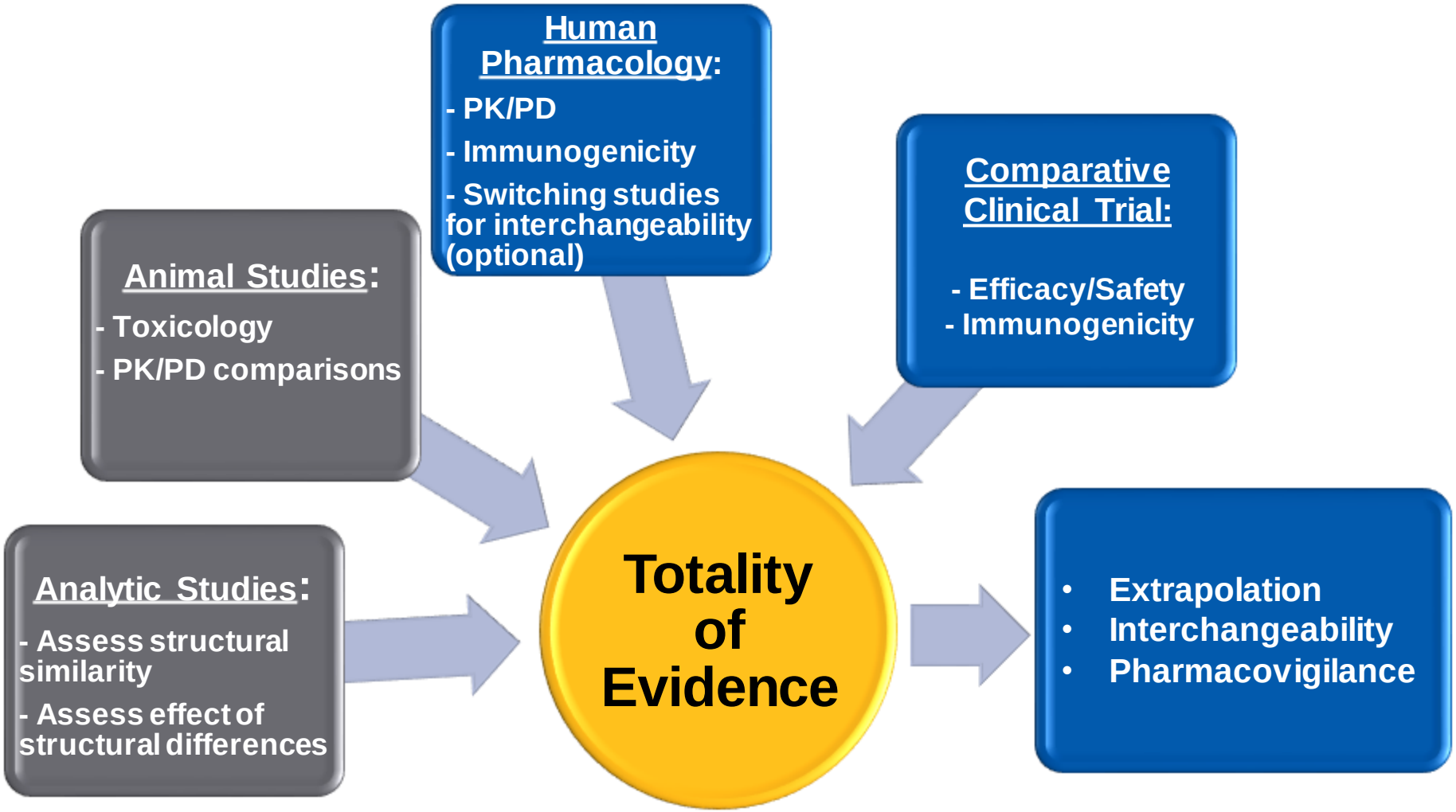
Biosimilar Approval: Totality of Evidence



At least one clinical comparative study to characterize efficacy, safety, and immunogenicity in a disease state

PD: pharmacodynamics; PK: pharmacokinetics.
Adapted from J Clin Oncol 2020; 2020;38(10):1070-1080.

Biosimilar Approval: No 'One Size Fits All' Approach



PD: Pharmacodynamics; PK: Pharmacokinetics.

https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval. Accessed 8/14/20.

Clinical Trials: Human Pharmacokinetics and Pharmacodynamics Study Design

- **Goal:** Demonstration of pharmacokinetic similarity to reference product
- **Study Design**: adequately sensitive populations to detect for clinically meaningful differences based on pharmacokinetic data
- **Data Analysis**: acceptable range is 80-125% (90% CI) for pharmacokinetic/pharmacodynamics parameters (i.e., AUC, C_{max}) compared with reference product
- **Other considerations:** immunogenicity should be characterized

https://www.fda.gov/files/drugs/published/FDA%E2%80%99s-Overview-of-the-Regulatory-Guidance-for-the-Development-and-Approval-of-Biosimilar-Products-in-the-US.pdf. Accessed 8/15/20.

Clinical Trials: Comparative Efficacy Trial Considerations

- **Goal:** confirm clinical equivalence using population and efficacy endpoints sensitive enough to detect product differences while minimizing impact of patient/disease differences
- **Study design:** Equivalence [two-sided] vs noninferiority [one-sided]
- **Population:** homogenous in terms of patient population/disease severity
- **Endpoints:** short-term clinical efficacy endpoint measuring pharmacologic activity (i.e., overall response rate)
- **Other considerations:** safety and immunogenicity

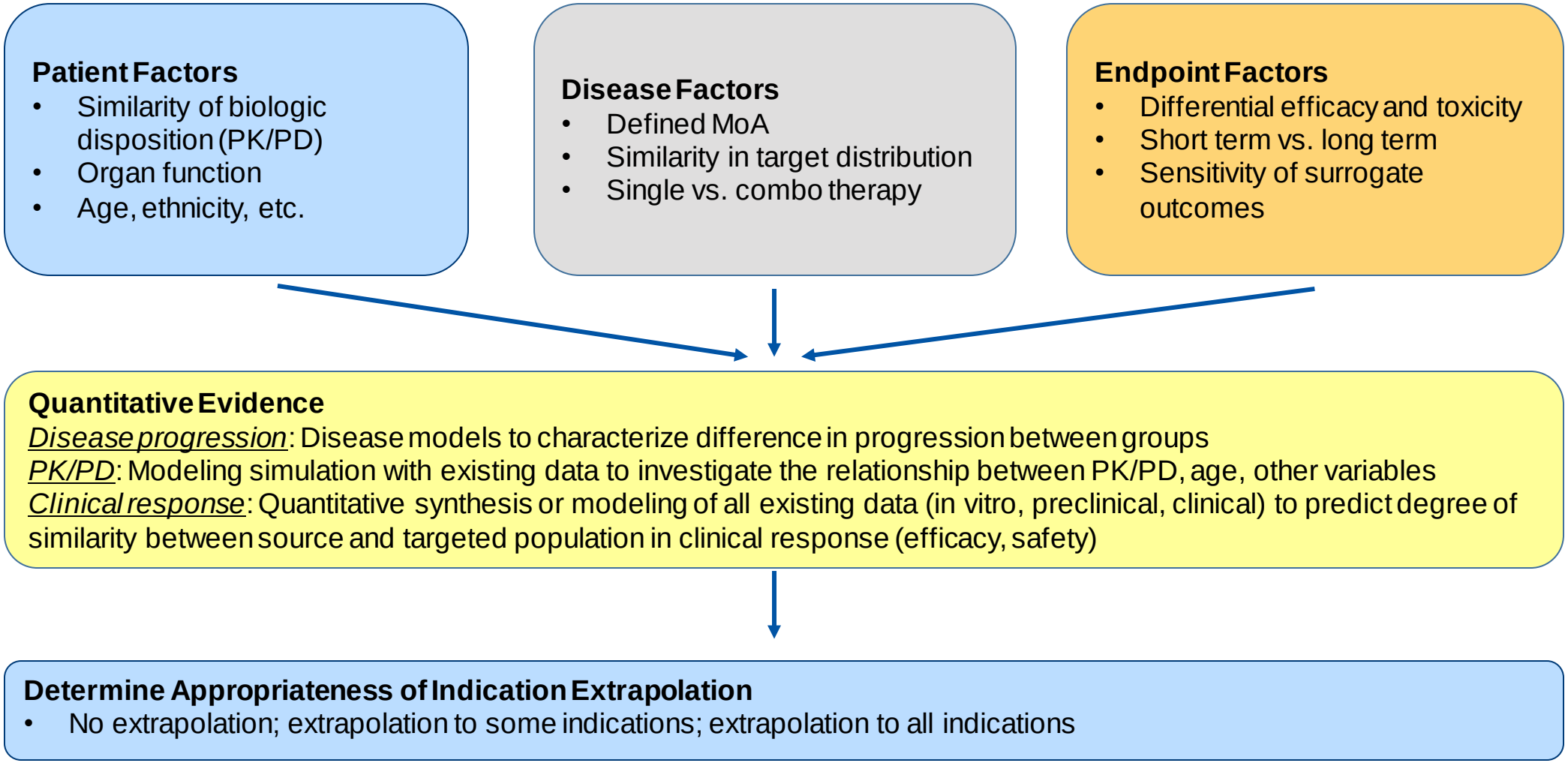
J Clin Oncol 2020;38(10):1070-1080.

Extrapolation

- Scientific justification of expanding biosimilar indications to other indications that were not directly studied by biosimilar manufacturer
- Extrapolation is not extending approval to multiple indications solely based on clinical data supporting one indication
- Scientific justification of extrapolation is based on:
  - All available data and information in biosimilar application
  - FDA's previous findings regarding safety and efficacy for other approved indications of reference product
  - Knowledge and consideration of various scientific factors for each indication

Food and Drug Administration. https://www.fda.gov/drugs/biosimilars/biosimilar-development-review-and-approval. Accessed 8/4/20.

Extrapolation Framework



MoA: mechanism of action; PD: pharmacodynamics; PK: pharmacokinetics.
Adapted from: J Natl Compr Canc Netw 2019;17(11.5):1424-1426.

Biosimilar Scenarios: Part II

- The chemotherapy regimen containing Xmab is submitted to CK's insurance company and the insurance responds that Xmab is not preferred any longer and CK should instead receive Xmab-abcd, a biosimilar product of Xmab.

- Can the pharmacist dispense Xmab-abcd in place of Xmab if CK's chemotherapy orders are written for Xmab? Does the order need to be changed to reflect Xmab-abcd?

Interchangeability

- BPCI Act allows for FDA-approved biosimilar to be substituted for a reference product without intervention of prescriber only if additional requirements are met:
  - Biosimilar is expected to produce the same clinical result as reference product in any given patient
  - Safety/efficacy of alternating or switching between biosimilar and RP is not greater than risk of using RP alone
- Biosimilars meeting these requirements will be designated as 'interchangeable' in the online Purple Book database (https://purplebooksearch.fda.gov/)
- No biosimilars currently considered interchangeable

BPCI: Biologics Pricing and Competition and Innovation Act; RP: Reference Product.
https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products. Accessed 8/5/20.

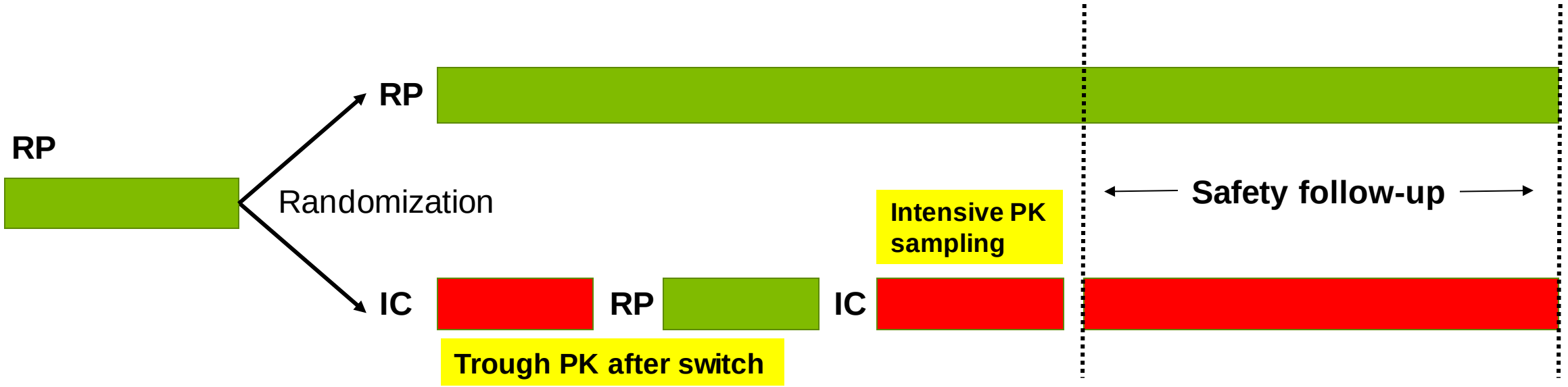
Interchangeability: FDA Guidance

Considerations for Industry per 2019 FDA Guidance
Product-Dependent Factors • Complexity/functional characterization • Immunogenicity risk
Post-Marketing Data • Relevant post-marketing data may be considered
Design/Analysis of Switching Studies • Efficacy/safety reported through assessment of differences in immunogenicity, pharmacokinetics, pharmacodynamics as compared to not switching
Comparator Product Considerations • US-licensed vs. non-US licensed comparators
Presentation Considerations • Same container closure system as reference product
Post-marketing Safety Monitoring (Pharmacovigilance)

https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-demonstrating-interchangeability-reference-product-guidance-industry. Accessed 8/5/20.

Interchangeability: Switching Study Design Principles

- Study endpoints assess impact of switching on PK/PD in a study population that is adequately sensitive to allow detection of differences in PK/PD, adverse effects, and immunogenicity
- Evaluate changes in treatment that result in **two or more alternating exposures:**



IC: Investigational Compound; PK: Pharmacokinetics; RP: Reference Product.
Adapted from https://www.fda.gov/media/112814/download. Accessed 8/15/20.

Pharmacovigilance

- WHO definition: Science and activities relating to the detection, evaluation, understanding, and prevention of adverse drug reactions (ADRs)
- Optimal workflow not outlined in FDA Biosimilar Action Plan although distinguishable names aid in expanding on existing framework
- Pharmacists are in a unique position to assist in monitoring and reporting “real-world” outcomes through audits, research, and adverse event reporting

Expert Opin Drug Saf 2020;19:229-232.
J Oncol Pharm Practice 2020;26(3):3-10.

Question 2: Which of the following is currently considered optional for an FDA biosimilar application?

A. Analytical studies
B. Pharmacokinetic studies
C. Comparative efficacy trial in at least one disease state
D. Switching studies for interchangeability

Factors Affecting Biosimilar Implementation

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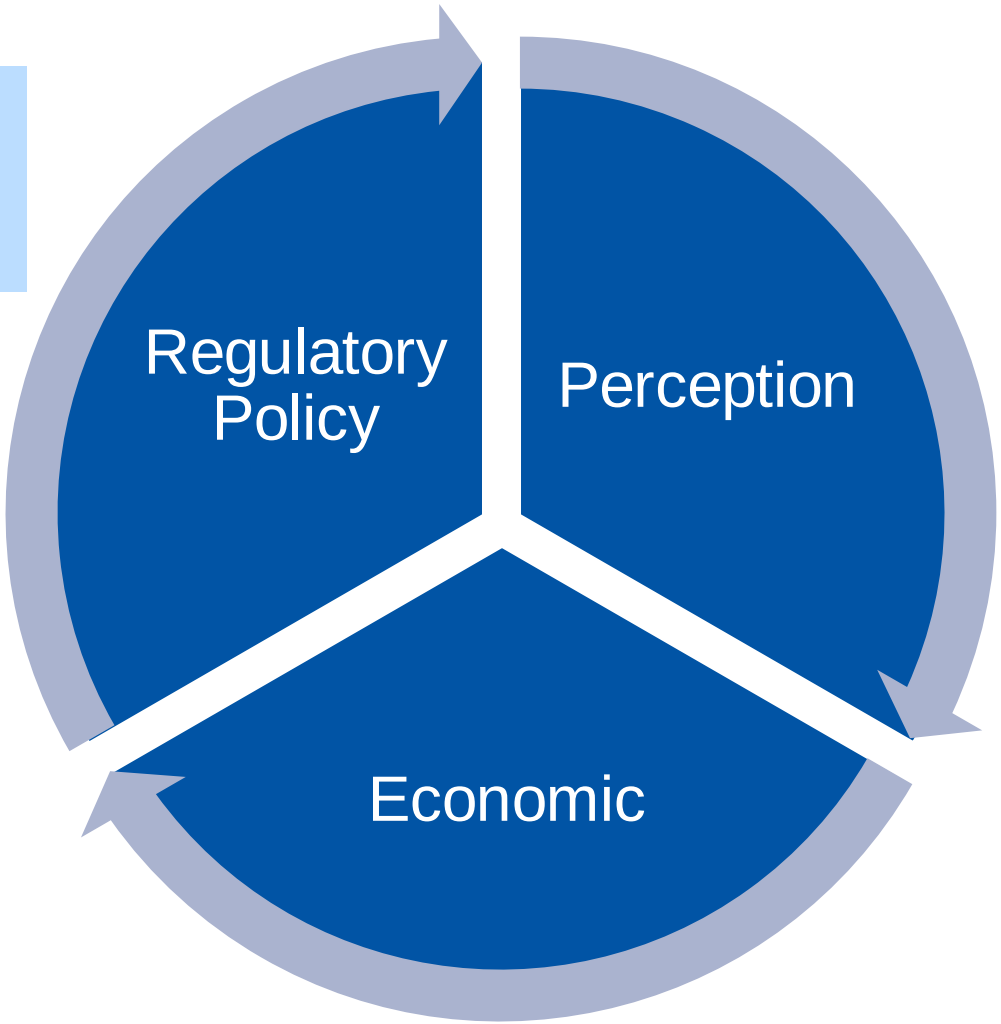
Factors Affecting Biosimilar Uptake in Oncology

- Approval process
- Interchangeability
- Extrapolation
- Pharmacovigilance



Treatment Goals:
- Curative
- Palliative

Prescriber:
- Interchangeability
- Extrapolation

Patient:
- Biosimilar education
- Financial responsibility

- Acquisition Cost
  - Site of care
  - 340b status
- Reimbursement models
  - Medicare/Medicaid
  - Commercial

J Clin Oncol 2018;36:1260-1265.
Oncologist 2018;23:1261-1265.
Am J Manag Care 2018;24(11 Suppl):S237-S243.

ASCO Position Statement: Prescriber Perspective

- Confidence in safety and efficacy: post-market surveillance
- Physicians and patients should be aware of product substitutions despite meeting interchangeability thresholds
- Clear naming and labeling of products for product distinction
- Ensure high-quality care while maintaining access through utilization of ASCO principles of coverage
- Peer reviewed education process via professional associations, online practice guidelines, and other educational materials for physicians and patients

J Clin Oncol 2018;36:1260-1265.

Global Pharmacy Perspective: Biosimilar Implementation

- Survey of members of the International Society of Oncology Pharmacy Practitioners (n=90):

Factors influencing biosimilar implementation
Medication cost/pricing
Available clinical data
Product availability
Healthcare provider preference

Challenges to biosimilar implementation
Prescriber reluctance/perceived inferiority
Resistance to switching established patients from to biosimilar product from reference product
Insurance company/funding source preference

- Conclusions: Education, standardization, and sharing of best practices are required for successful biosimilar implementation for hematology/oncology use

J Oncol Pharm Practice 2020;26(3):22–32.

Managed Care Perspective: Biosimilar Implementation

- Survey of managed care and specialty pharmacy professionals (n=300) ranking most important strategies to overcoming barriers to biosimilar implementation:

Highest-rated strategies	Lowest-rated strategies
Prescriber education regarding switching studies (91%)	Utilizing quotas to incentivize providers to prescriber biosimilars (40%)
FDA guidance on pharmacy-level substitution of reference biologics with biosimilars (90%)	Requiring therapeutic drug monitoring for patients who switch to biosimilars (39%)

J Manag Care Spec Pharm 2019;25(8): 904-912.

Challenges to Biosimilar Implementation

- Prescriber and patient communication/education
- Multiple biosimilars for same reference product
  - Medication error potential
  - Pharmacy space limitations
- No currently designated interchangeable products
- Confusion due to differences in product presentation between biosimilars and other proprietary products
- Reimbursement structure for different payers/preferred payer formularies

Am J Health-Syst Pharm. 2019; 76:1725-1738.

Question 3: Which of the following is not considered a current challenge to biosimilar implementation in oncology?

A. Pharmacy space limitations
B. Differences in product presentation
C. Several interchangeable biosimilar products are available
D. Reimbursement differences among different payers

Logistical Considerations for Biosimilar Implementation

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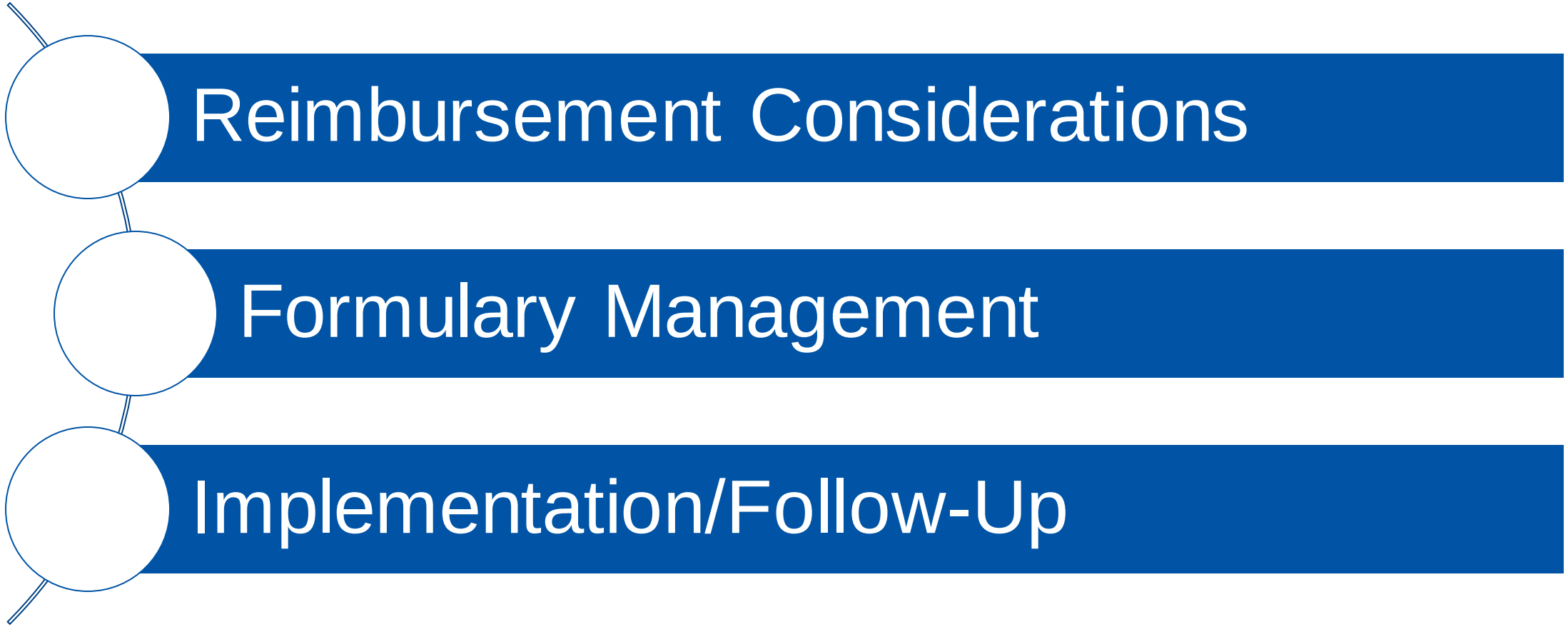
Biosimilar Scenarios: Part III

- Several biosimilars are now on the market for Xmab and hospital/pharmacy leadership wants to know the plan for biosimilar implementation

- What considerations should be part of the plan?

Logistics: Make a Plan for Success



Reimbursement: Commercial Insurance

- Biosimilar policy decisions from 17 largest health plans in August 2019:

Biosimilar Decision (n=535)	Proportion
Biosimilar product preferred	14%
Reference product preferred	33%
No preference	53%

- Despite differences in unit cost from reference product, negotiations may need to occur to get savings discount
- Preferred status may be established by payer
- Recommendation: Know your payer mix to determine current biosimilar coverage policies

JAMA. 2020;323(19):1972-1973.
PT 2019;44(3):54-63.

Reimbursement: Medicare Part B

Day 0 ⬇ OPPS ⬇ ASP Est ⬇ 3 years ⬇

	Provider Type	Biosimilar Launches	OPPS Transitional Pass-through Status Effective	CMS Average Sales Price (ASP) Established
Medicare Part B Reimbursement Methodology	Non-340B Hospitals	Biosimilar WAC + 3% Biosimilar WAC		Biosimilar ASP + 6% Originator ASP
	340B Hospitals	Biosimilar WAC -22.5% Biosimilar WAC	Biosimilar WAC + 3% Biosimilar WAC	
	Clinic	Biosimilar WAC + 3% Biosimilar WAC		

CMS: Center for Medicare and Medicaid Services; OPPS: Outpatient Prospective Payment System; WAC: Wholesale Acquisition Cost.

https://www.federalregister.gov/documents/2018/11/21/2018-24243/medicare-program-changes-to-hospital-outpatient-prospective-payment-and-ambulatory-surgical-center. Accessed 8/18/20.
https://www.coheruscomplete.com/assets/documents/0519_COH_P142r1_Biosimilar_reimbursment_061919_v24%20FINAL.pdf. Accessed 8/18/20.

Healthcare Systems: Formulary Considerations

- Available clinical evidence for indication and for extrapolation depending on requested indication(s)
  - Consider establishing preferred biosimilars
- Economic impact based on institution-specific factors
  - Financial analysis of projected cost and reimbursement
- Infrastructure requirements for implementation
  - Formulary substitution process
  - Reimbursement/access support
  - Electronic health records/order sets
  - Medication safety tracking mechanisms

Am J Health-Sits Pharm. 2019; 76:1725-1738.

Pharmacist Impact on Formulary Submissions

Formulary Evaluation

- P&T submission/literature review
- Establish pharmacy role in health system substitution policy
- Estimate usage/financial analysis assistance

Implementation

- Order set updates/create infrastructure for additional biosimilar products for same reference product
- Outline biosimilar conversion plan
- Prepare educational materials for prescribers, infusion staff, patients

Pharmacovigilance

- Conduct periodic medication usage evaluations
- Report medication-related adverse events
- Review FDA updates

Pharmacy Considerations in Biosimilar Implementation

- **Patient management**
  - Insurance-preferred biosimilar navigation
  - Patient assistance program facilitation
- **Operations/inventory management**
  - **Shortages:** evaluate potential for drug shortage risk
  - **Shelf space:** preferred stocked biosimilar vs on demand
  - **Medication error prevention:** aggregate by brand name vs. generic name if multiple products; design label with brand names included if possible; infusion rate guardrails
- **Contracting/revenue management**
  - Drug acquisition cost/site of care
  - Ongoing financial assessments

Am J Health-Syst Pharm. 2019; 76:1725-1738.

Future of Biosimilars

- Pharmacoeconomic assessments
- Key stakeholder collaboration to maximize cost savings and expand access to patients
- Expand available education sources for clinicians and patients to increase biosimilar uptake
- Focus on expanding pharmacovigilance framework for quality assurance

Drugs 2020;80:99-113.

Conclusions

- Biosimilars are here – best preparation is creation of infrastructure process to navigate changes as safely and efficiently as possible

- Pharmacists are well-positioned to support resolving biosimilar implementation challenges in terms of education, operations, financial management, and pharmacovigilance

Questions?