Biosimilar Implementation in Hematology/Oncology

Amber Lawson, PharmD, BCOP
Pharmacy Program Coordinator
UK Healthcare
Associate Adjunct Professor
UK College of Pharmacy
Lexington, Kentucky
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
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
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:

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

<table>
<thead>
<tr>
<th>FDA Biosimilar Action Plan Key Elements</th>
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<tbody>
<tr>
<td>✓ Improve efficiency of biosimilar and interchangeable product development and approval process</td>
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<tr>
<td>✓ Maximize scientific and regulatory clarity for biosimilar development</td>
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<tr>
<td>✓ Develop effective communications to improve understanding of biosimilars among patients, clinicians, payers</td>
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<tr>
<td>✓ Support market competition by reducing attempts to unfairly delay competition</td>
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FDA: Food and Drug Administration.  
# FDA-Approved Oncology Biosimilars in 2020

<table>
<thead>
<tr>
<th>Supportive Care</th>
<th>Reference Product</th>
<th>Biosimilar Products</th>
</tr>
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</table>
|                | Filgrastim (Neupogen®) | • Filgrastim-aafi (Nivestym®)  
 |                |                     | • Filgrastim-sndz (Zarxio®)  
 |                | Pegfilgrastim (Neulasta®) | • Pegfilgrastim-apgf (Nyvepria®)  
 |                |                     | • Pegfilgrastim-bmez (Ziextenso®)  
 |                |                     | • 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™)  

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
Biosimilar Approval: Totality of Evidence

PD: pharmacodynamics; PK: pharmacokinetics.

At least one clinical comparative study to characterize efficacy, safety, and immunogenicity in a disease state
Biosimilar Approval: No ‘One Size Fits All’ Approach

**Totality of Evidence**

- **Analytic Studies**: Assess structural similarity, Assess effect of structural differences
  - **Human Pharmacology**:
    - PK/PD
    - Immunogenicity
    - Switching studies for interchangeability (optional)
  - **Comparative Clinical Trial**:
    - Efficacy/Safety
    - Immunogenicity
  - Animal Studies: Toxicology, PK/PD comparisons
  - **Extrapolation**
  - **Interchangeability**
  - **Pharmacovigilance**

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<sub>max</sub>) compared with reference product

- **Other considerations:** immunogenicity should be characterized
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
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

**Extrapolation Framework**

**Patient Factors**
- Similarity of biologic disposition (PK/PD)
- Organ function
- Age, ethnicity, etc.

**Disease Factors**
- Defined MoA
- Similarity in target distribution
- Single vs. combo therapy

**Endpoint Factors**
- Differential efficacy and toxicity
- Short term vs. long term
- Sensitivity of surrogate outcomes

**Quantitative Evidence**
- **Disease progression**: Disease models to characterize difference in progression between groups
- **PK/PD**: Modeling simulation with existing data to investigate the relationship between PK/PD, age, other variables
- **Clinical response**: Quantitative synthesis or modeling of all existing data (in vitro, preclinical, clinical) to predict degree of similarity between source and targeted population in clinical response (efficacy, safety)

**Determine Appropriateness of Indication Extrapolation**
- No extrapolation; extrapolation to some indications; extrapolation to all indications
Biosimilar Scenarios: Part II

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

• Can the pharmacist dispense Xmb-abcd in place of Xmb if CK’s chemotherapy orders are written for Xmb? Does the order need to be changed to reflect Xmb-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
## 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)

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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**:

![Diagram showing study design principles with labels: IC, RP, Trough PK after switch, Intensive PK sampling, Safety follow-up.]

IC: Investigational Compound; PK: Pharmacokinetics; RP: Reference Product.
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

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
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

Oncologist 2018;23:1261-1265.
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
Global Pharmacy Perspective: Biosimilar Implementation

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

<table>
<thead>
<tr>
<th>Factors influencing biosimilar implementation</th>
<th>Challenges to biosimilar implementation</th>
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<tbody>
<tr>
<td>Medication cost/pricing</td>
<td>Prescriber reluctance/perceived inferiority</td>
</tr>
<tr>
<td>Available clinical data</td>
<td>Resistance to switching established patients from to biosimilar product from reference product</td>
</tr>
<tr>
<td>Product availability</td>
<td>Insurance company/funding source preference</td>
</tr>
<tr>
<td>Healthcare provider preference</td>
<td></td>
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</tbody>
</table>

- Conclusions: Education, standardization, and sharing of best practices are required for successful biosimilar implementation for hematology/oncology use.
Survey of managed care and specialty pharmacy professionals (n=300) ranking most important strategies to overcoming barriers to biosimilar implementation:

<table>
<thead>
<tr>
<th>Highest-rated strategies</th>
<th>Lowest-rated strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prescriber education regarding switching studies (91%)</td>
<td>Utilizing quotas to incentivize providers to prescriber biosimilars (40%)</td>
</tr>
<tr>
<td>FDA guidance on pharmacy-level substitution of reference biologics with biosimilars (90%)</td>
<td>Requiring therapeutic drug monitoring for patients who switch to biosimilars (39%)</td>
</tr>
</tbody>
</table>
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
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
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 Considerations
- Formulary Management
- Implementation/Follow-Up
Reimbursement: Commercial Insurance

• 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

<table>
<thead>
<tr>
<th>Biosimilar Decision (n=535)</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biosimilar product preferred</td>
<td>14%</td>
</tr>
<tr>
<td>Reference product preferred</td>
<td>33%</td>
</tr>
<tr>
<td>No preference</td>
<td>53%</td>
</tr>
</tbody>
</table>
# Reimbursement: Medicare Part B

<table>
<thead>
<tr>
<th>Provider Type</th>
<th>Biosimilar Launches</th>
<th>OPPS Transitional Pass-through Status Effective</th>
<th>CMS Average Sales Price (ASP) Established</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medicare Part B Reimbursement Methodology</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Medicare Part B Hospitals</td>
<td>Non-340B Hospitals</td>
<td>Biosimilar WAC + 3% Biosimilar WAC</td>
<td>Biosimilar ASP + 6% Originator ASP</td>
</tr>
<tr>
<td>340B Hospitals</td>
<td>Biosimilar WAC -22.5% Biosimilar WAC</td>
<td>Biosimilar WAC + 3% Biosimilar WAC</td>
<td></td>
</tr>
<tr>
<td>Clinic</td>
<td>Biosimilar WAC + 3% Biosimilar WAC</td>
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CMS: Center for Medicare and Medicaid Services; OPPS: Outpatient Prospective Payment System; WAC: Wholesale Acquisition Cost.


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
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
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
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?