Biosimilars in the United States: Current status, barriers to utilization, and a growing evidence base to support treatment and coverage decisions

Cate Lockhart, MS, PharmD, PhD
Executive Director, BBCIC
October 10, 2019
Outline

- It All Started with Generics
- Then Came Biosimilars
- Barriers to Biosimilars
- Data Sources for Decision Makers
- BBCIC: Research Progress
It All Started With Generics
History of Generic Drugs in the U.S.

1984

History of Generic Drugs in the U.S.

Hatch-Waxman Act

1984
1989
2002
2008
2017

ANDA
Market Exclusivity

GENERIC PRESCRIPTIONS (% of total)

33% 53% 72% 90%


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Adverse Events

470 ANDAs filed

1069 ANDAs filed

Investigation by House Energy and Commerce = Multiple convictions of FDA officials, manufacturers, consultants for bribery

Manufacturers discovered to be falsifying data


Generic Drug Enforcement Act

Kesselheim AS. CMAJ 2011;183(12):1350-1351.
Adverse Events

Hatch-Waxman Act

Meanwhile...

1984

Generic Drugs

Market Exclusivity

“Pay-To-Delay”

Kesselheim AS. CMAJ 2011;183(12):1350-1351.
Economic Impact of Generics in the U.S.

Prescriptions filled with generics in 2017

- 90%

Prescription drug spending attributed to generics

- 23%

Savings to U.S. healthcare system in the past decade

- $1.6 trillion

Savings to the U.S. healthcare system in 2017 alone

- $265 billion
Then Came Biosimilars...
Biosimilars in the U.S.

Biologics Price Competition and Innovation Act of 2009 (BPCIA)

Abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product

351(k) Application

2010
Requirements for FDA Registration

Demonstrating Biosimilarity → TOTALITY of EVIDENCE

Analytical

Demonstrate the product is “highly similar” to the reference product

Non-Clinical

Toxicity

Clinical Pharmacology

Clinical study to assess immunogenicity and PK/PD showing safety/purity/potency in at least 1 relevant indication

Additional Clinical Studies

If necessary

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https://www.fda.gov/biosimilars
Biosimilars Approved in US – as of Sept. 2019

- **2015**
  - **Renflexis®** (infliximab-abda)
  - Lusduna™ (insulin glargine)*
  - Cyltezo™ (adalimumab-abdm)
  - **Mvasi®** (trastuzumab-awwb)
  - Ogivri™ (trastuzumab-dkst)
  - **Admelog®** (insulin lispro)*
    - Ixifi™ (infliximab-qbtx)
  - Zarfitor™ (trastuzumab-dttb)
  - Trazimera™ (trastuzumab-qyyp)
  - **Kanjinti®** (trastuzumab-anins)
    - Ziraveg™ (bevacizumab-bvzr)
    - Ruxience™ (rituximab-pvvr)
    - Hyrimoz™ (adalimumab-bwwd)

- **2016**
  - **Zarxio®** (filgrastim-sndz)
  - Erelzi™ (etanercept-szzs)
  - Amjevita™ (adalimumab-atto)

- **2017**
  - **Basaglar®** (insulin glargine)*
  - Inflectra® (infliximab-dyyb)
  - Retacrit® (epoetin alfa-epbx)
  - Fulphila® (pegfilgrastim-jmdb)
  - Nivestym® (filgrastim-aafi)
  - Hyrimoz™ (adalimumab-adaz)

- **2018**
  - **Basaglar®** (insulin glargine)*
  - **Inflectra®** (infliximab-dyyb)
  - **Retacrit®** (epoetin alfa-epbx)
  - **Fulphila®** (pegfilgrastim-jmdb)
  - **Nivestym®** (filgrastim-aafi)
  - **Hyrimoz™** (adalimumab-adaz)

- **2019**
  - **Udenyca®** (pegfilgrastim-cbqv)
  - **Ruxience™** (rituximab-pvvr)
  - **Truxima™** (rituximab-abb)
  - **Herzuma™** (trastuzumab-pkrb)

*FDA approval as a follow-on biologic


Biosimilar Sales

Sales of Biologics and Biosimilars in the U.S. and Europe

- United States: 59% Biologic Sales, 2% Biosimilar Sales
- Europe: 87% Biologic Sales, 22% Biosimilar Sales
- Japan: 6% Biologic Sales, 7% Biosimilar Sales
- Other: 13% Biologic Sales, 4% Biosimilar Sales

Barriers to Biosimilar Utilization
Who are the stakeholders for biosimilars in the United States?
Biosimilars – The Players

• Who are the stakeholders for biosimilars in the United States?
Factors Influencing U.S. Biosimilar Utilization

Legislation Finally in Place: BPCIA

Criticisms:
- Delay in FDA Guidance
- Slow approvals by FDA
- CMS policy
- FDA naming policy

2010
1. Improving the efficiency of the biosimilar and interchangeable product development and approval process;

2. Maximizing scientific and regulatory clarity for the biosimilar product development community;

3. Developing effective communications to improve understanding of biosimilars among patients, clinicians, and payors; and

4. Supporting market competition by reducing gaming of FDA requirements or other attempts to unfairly delay competition.

Biosimilars – The Players

Who are the stakeholders for biosimilars in the United States?

- Regulators
- Manufacturers
- Payers
- Prescribers
- Health Systems
- Other Healthcare Providers
- Patients
- Other Healthcare Providers

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Factors Influencing U.S. Biosimilar Utilization

BPCIA → Market Tactics

- "Pay-To-Delay"
- Contracting
- Patent Litigation

2010

Biosimilars

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Biosimilars – The Players

- Regulators
- Manufacturers
- Health Systems
- Payers
- Prescribers
- Other Healthcare Providers
- Patients
- Other Healthcare Providers

Who are the stakeholders for biosimilars in the United States?
Factors Influencing US Biosimilar Utilization

**Uncertainty - Prescribers**

- **297 US physicians** in specialties that are high biologics prescribers
  - Rheumatologists
  - Dermatologists
  - Gastroenterologists

- **Survey** of experience and attitudes around non-medical switching to a biosimilar

<table>
<thead>
<tr>
<th>Percentage</th>
<th>Statement</th>
</tr>
</thead>
<tbody>
<tr>
<td>63%</td>
<td>Not enough long-term data to be comfortable prescribing</td>
</tr>
<tr>
<td>44%</td>
<td>Trust biosimilars are safe</td>
</tr>
<tr>
<td>42%</td>
<td>Taking a biosimilar is more risky than an originator</td>
</tr>
<tr>
<td>33%</td>
<td>Trust biosimilars are effective for individuals, not just groups</td>
</tr>
<tr>
<td>31%</td>
<td>Comfortable with a different FDA process for biosimilars</td>
</tr>
<tr>
<td>30%</td>
<td>Comfortable with approval by extrapolation</td>
</tr>
</tbody>
</table>

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Factors Influencing U.S. Biosimilar Utilization

- Prescribers

- 1,201 US physicians in specialties that are high biologics prescribers

- 75% trust the FDA approval decisions, but...

- When asked if they believe biosimilars are safe and appropriate for naïve and existing patients....
Factors Influencing US Biosimilar Utilization

Uncertainty - Prescribers


**Global themes:**

- More comfortable with initiating biosimilars in naïve patients than switching stable patients
- Generally NOT comfortable with indication extrapolation
- Level of biosimilar knowledge varied, but the majority were unsure
Factors Influencing US Biosimilar Utilization

- **1,696 US patients** with rheumatoid arthritis, Chrohn’s, ulcerative colitis, psoriasis, psoriatic arthritis currently taking a biologic

Factors Influencing US Biosimilar Utilization

Uncertainty

....and other studies

Post-approval studies evaluating comparative safety and effectiveness are critical to generating real-world evidence to inform clinical practice and policy decisions

OPPORTUNITY FOR EDUCATION
Biosimilars: Data Sources for Decision-Makers
Data Sources – Real World Evidence

RWE and Regulatory Use

21st Century Cures requires FDA to establish a program to evaluate potential use of RWE for approval of new indications or to satisfy post-approval study requirements, label expansion or revision, and benefit/risk profiles.

“The FDA uses RWE for regulatory decisions, albeit primarily related to safety. Nevertheless, for some drugs, the demonstration of efficacy has been based on RWE from case series or registries.” – Jarrow et al.

“Multiple converging sub-studies from the same populations, or independent studies combining multiple data sources, could bring real-world data closer to ‘causality’ and could be perceived as acceptable alternatives to randomized trials.” - Greenfield

“…on average, there is little evidence for significant effect estimate differences between observational studies and RCTs, regardless of specific observational study design, heterogeneity, or inclusion of studies of pharmacological interventions.” – Anglemyer et al.

Greenfield. Value in Health 2017;20:1023-4
Real world evidence development initiatives are focused on expanding evidence effectively, rapidly and cost effectively (e.g., FDA EvGen, PCORI, NIH Collaboratory).

**6-7 years & $0.8B-$1.2B on a few thousand patients**

**CONSEQUENCE**
- Great variation between study cohorts and real-world population
- Resistance from payers to reimburse for new therapies
- Hesitation of physician to prescribe therapy
- Undetermined real-world effectiveness of treatments

<table>
<thead>
<tr>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Phase 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>20-100 healthy volunteers</td>
<td>100-500 patients with target condition</td>
<td>1000-5000 patients with target condition</td>
<td>Post-marketing research and monitoring</td>
</tr>
</tbody>
</table>

Real-world utilization quickly outpaces available clinical evidence.
Real-World Data Sources

- **Study Types**
  - Pragmatic Clinical Trials
  - Prospective Observational Studies
  - Registry Studies
  - Retrospective Database Studies
  - Case Reports

- **Data Sources**
  - Pragmatic or Prospective Trials
    - Administrative Claims
    - Electronic Health Records
    - Patient-Reported/Self-Generated
  - Registries
Strength of Secondary Data

Patient interaction with the U.S. healthcare system generates data

Why is data collected?

- Payment/billing
- Document clinical care
- Physician decision support
- Recordkeeping
- Registries
- Rich source of information for patient safety evaluations

Commonly Used Data Sources

- Administrative Claims
- Electronic Medical Records

Real World Evidence

Limitations:

- Data is usually collected for reasons OTHER THAN research, NOT RANDOMIZED
- Longitudinal: Requires consistent care in one healthcare delivery system and/or insurance plan
- Clinical outcomes: may not be readily identified
- Market uptake: influences research capability
- Coding: Non-specific codes or errors

Patient-Generated Data

- Not just a PRO Instrument anymore...
  - Wearable devices
  - Mobile phone applications
  - Social Media
  - Mobile app
  - Social Media
  - Electronic Health Record
  - Administrative Claims
  - Enriched Data

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Patient-Generated Data

Limitations:

- Requires careful privacy protections
- Subject to recall bias and other reporting errors
- Requires active and willing participation
- Must be able to LINK DATA to a longitudinal source (administrative claims) or electronic medical record to be useful
BBCIC:
One Approach to
Real-World Evidence Generation
A non-profit, multi-stakeholder, collaborative, scientific public service initiative conducting rigorous post-marketing observational research to monitor biosimilar products and novel biologics for effectiveness and safety in a real-world setting
The AMCP BBCIC strategy provides a unique opportunity for Managed Care to support public knowledge of biologic and biosimilar drugs with robust science.

- BBCIC leverages the Sentinel Initiative
  - Improves the efficiency and cost-effectiveness of post-marketed observational studies.

- BBCIC actively monitors biosimilars and innovators
  - Anonymous data from ~95 million patients

- BBCIC is a multi-stakeholder collaboration
  - Diverse expertise allows for a larger voice with more credibility

A forum for collaboration between managed care organizations, integrated delivery networks, PBMs, pharma companies and research institutions

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• The BBCIC Charter outlines transparent organized process for conducting research. There are no surprises.

• CER protocols, designed by KOLs and following ISPOR-ISPE guidelines, must explicitly pre-specify the epidemiologic, statistical and clinical thresholds required to identify a safety-related finding.

• 18 founding participants including Managed Care Organizations, Integrated Delivery Networks, PBMs & Harvard-Pilgrim Health Care Institute

• Public representatives on Planning Board: ASCO, American College of Rheumatology, National Health Council
BBCIC Progress to Date

**June 2015**
Consortium officially kicked off

**October 2015**
Governance approved

**February 2016**
First research plan approved
Three research protocols initially registered on [http://www.clinicaltrials.gov](http://www.clinicaltrials.gov)

**Q3 2016**
Four research teams convened

**Q3 2017**
Descriptive analyses conclude

**Q4 2017**
Switching and NDC/J-Code Workgroups convened
Descriptive analysis publications in preparation

**Q1 2018**
CER Methods and ICD-10 Conversion Workgroups convened

**Q3 2018**
Switching Methods recommendations submitted for publication

**Q2 2019**
Four manuscripts published, another four in peer-review

**Q3 2019**
Convene Oncology data feasibility and descriptive analysis Workgroup
Convene G-CSF Comparative Safety and Effectiveness Workgroup

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• Data fitness / infrastructure
  – Data availability and characterization
    • Capture of NDC information on medical claims
  – Impact of transition from ICD-9 to ICD-10, claims-based algorithms

• Descriptive studies

• Study design and methods
  – Switching study design and analytic approaches
  – Comparative safety/effectiveness study design and analytic approaches

• Protocol-Driven Comparative Safety/Effectiveness Studies
BBCIC - Progress

- What we have **DONE**
- What we are **DOING**
- What we **PLAN** to **DO**
• What we have **DONE**

• What we are **DOING**

• What we **PLAN** to **DO**
### Completed Projects - Descriptive Analysis

<table>
<thead>
<tr>
<th>Project</th>
<th>Objective</th>
<th>Of Note</th>
</tr>
</thead>
</table>
| Insulins                 | Describe treatment patterns and outcomes of adults with diabetes treated with long- or intermediate-acting insulin                                                                                       | • Rates consistent with other studies  
• Algorithms and robust methods required to more reliably identify cohorts                                                                                                                         |

**Harnessing the Biologics and Biosimilars Collective Intelligence Consortium to Evaluate Patterns of Care**

Cheryl N. McMahl-Walraven, MSW, PhD; Daniel J. Kent, BSPharm, PharmD, CDE; Catherine A. Panozzo, PhD, MPH; Pamala A. Pawloski, PharmD, BCOP, FCCP; Kevin Haynes, PharmD, MSCE; James Marshall, MPH; Jeffrey Brown, PhD, MA; Bernadette Eichelberger, PharmD; and Catherine M. Lockhart, MS, PharmD, PhD

*J Manag Care Spec Pharm.* Published online August 2019.  

**Descriptive Analysis of Long- and Intermediate-Acting Insulin and Key Safety Outcomes in Adults with Type 2 Diabetes Mellitus**

Daniel J. Kent, BSPharm, PharmD, CDE; Cheryl N. McMahl-Walraven, MSW, PhD; Catherine A. Panozzo, PhD, MPH; Pamala A. Pawloski, PharmD, BCOP, FCCP; Kevin Haynes, PharmD, MSCE; James Marshall, MPH; Jeffrey Brown, PhD, MA; Bernadette Eichelberger, PharmD; and Catherine M. Lockhart, MS, PharmD, PhD

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# Completed Projects - Descriptive Analysis

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<tr>
<td><strong>Erythropoietin Stimulating Agents (ESAs)</strong></td>
<td>Feasibility assessment of comparability between BBCIC data and the U.S. Renal Data System (USRDS) in evaluating outcomes in hemodialysis patients</td>
<td><em>BBCIC hemodialysis population is similar to the USRDS in age and sex distributions, but is <strong>not</strong> sufficiently similar in duration of dialysis.</em></td>
</tr>
</tbody>
</table>
| **Granulocyte Colony Stimulating Factors (G-CSFs)** | Describe utilization, characteristics, and outcomes in patients receiving GCSF treatment as neutropenia prophylaxis due to high-risk chemotherapy regimens                                                                 | *Initial evidence that cohorts and outcomes of interest can be identified in the BBCIC data network*  
*Foundation for comparative studies*                                                                                                               |
| **Anti-Inflammatories**          | Describe treatment patterns and outcomes among patients with autoimmune diseases treated with biologic therapy                                                                                           | *Measuring effectiveness is challenging beyond surrogates such as dosage or therapy change*  
*Exploring enriching data linkages*                                                                                                                   |

**Manuscripts in Preparation or Undergoing Peer-Review**

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### Completed Projects – Methods/Infrastructure

<table>
<thead>
<tr>
<th>Project</th>
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<tbody>
<tr>
<td>Switching Methods</td>
<td>Best practices and recommendations for treatment of medication switching or sequencing as a covariate or confounder in future BBCIC studies</td>
</tr>
</tbody>
</table>

Methodologic considerations for noninterventional studies of switching from reference biologic to biosimilars

Rishi J. Desai¹ | Seoyoung C. Kim¹ | Jeffrey R. Curtis² | Jaclyn L.F. Bosco³ | Bernadette Eichelberger⁴ | Charles E. Barr⁴ | Catherine M. Lockhart⁴ | Brian D. Bradbury⁵ | Jerry Clewell⁶ | Hillel P. Cohen⁷ | Joshua J. Gagne¹ |

on behalf of the Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) Switching Workgroup

## Completed Projects – Methods/Infrastructure

<table>
<thead>
<tr>
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<tr>
<td>CER Methods</td>
<td>Best practices and recommendations for conducting robust, large-scale, observational comparative safety and effectiveness research in the BBCIC</td>
</tr>
<tr>
<td>ICD-10 Mapping</td>
<td>Recommended methods and complete conversion of ICD-9-CM codes to ICD-10-CM codes for all diseases of current interest to the BBCIC</td>
</tr>
<tr>
<td>NDC/J-Code Use</td>
<td>Investigate the extent to which NDC codes, and product-specific J-Codes, are reported in physician-office medical claims for drugs administered in the clinic</td>
</tr>
</tbody>
</table>

**Manuscripts in Preparation or Undergoing Peer-Review**
• Outcome rates were consistent with other clinical and observational studies.
• With the BBCIC DRN we are able to reliably identify and characterize exposures, outcomes, and potential confounders for the disease cohorts of interest.
• Improved methods and data infrastructure will enrich BBCIC research capabilities

Barriers and facilitators to conduct high-quality, large-scale safety and comparative effectiveness research: The Biologics and Biosimilars Collective Intelligence Consortium experience

Catherine M. Lockhart\textsuperscript{1} \textsuperscript{ID} | Cara L. McDermott\textsuperscript{1} | Thomas Felix\textsuperscript{2} | Nancy D. Lin\textsuperscript{3} \textsuperscript{ID} | Mark J. Cziraky\textsuperscript{4} | Aaron B. Mendelsohn\textsuperscript{5} | Jeffrey S. Brown\textsuperscript{5}

2018 Presentations

5 Podium Presentations
- ICPE
- ISPOR
- DIA
- AMCP Nexus
- NW AMCP

7 Poster Presentations
- HCSRN
- ICPE
- AMCP Nexus
2019 Presentations

6 Podium Presentations

- CBI
- BioTech
- ISPOR
- ICPE
- DIA Biosimilars
- AMCP Nexus

6 Poster Presentations

- HCSRN
- AMCP Annual
- ISPOR
- ICPE
- AMCP Nexus
• What we have DONE

• What we are DOING

• What we PLAN to DO
Background and Rationale
For over two decades, recombinant human granulocyte colony-stimulating factors (G-CSFs) have been used to treat and prevent chemotherapy-induced neutropenia. Currently two biosimilar products to reference filgrastim (filgrastim-sndz, filgrastim-aafi), and two biosimilars to reference pegfilgrastim (pegfilgrastim-jmdb, pegfilgrastim-cbqv) have been approved in the US. Building upon a previous BBCIC descriptive analysis, we are starting our first Comparative Effectiveness Research (CER) project focused on G-CSFs.
ONCOLOGY FEASIBILITY AND DATA FITNESS

Principal Investigator:
• Nancy Lin, ScD - Senior Scientist, Optum Epidemiology

The BBCIC has begun a new infrastructure project to identify, evaluate, and test potential new data sources to enrich the BBCIC distributed research network (DRN) capabilities in conducting robust, cancer-specific safety and effectiveness research.

Background and Rationale
A marked increase in the approval of biosimilar products, particularly in cancer therapy, is anticipated as a result of patent expirations for a number of originator biologics. As such, there is a need to generate robust real-world evidence for biosimilar cancer therapeutics. Given the number of biosimilars in oncology expected to be considered for approval in the near future, BBCIC is establishing the necessary resources to do product- or disease-specific comparative effectiveness research.
• What we have DONE

• What we are DOING

• What we PLAN to DO
Potential BBCIC Research

- Insulins Comparative Safety and Effectiveness
- Trastuzumab Descriptive Analysis
- Bevacizumab Descriptive Analysis
- Evaluation of Switching and Treatment Patterns in Rheumatoid Arthritis
- Feasibility Analysis of an Electronic Medical Records Research Network

BBCIC Committees are actively identifying new research topics

NOTE: The annual research agenda is not finalized until voted on and approved by the BBCIC Science Committee and Planning Board. All BBCIC Participants have a seat on both committees to guide BBCIC research. These projects represent a selection of current interests of the BBCIC, but is not an exhaustive list and may not yet be prioritized on the research agenda.

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Practical Application of BBCIC Research

WHAT WE PROVIDE:

REAL-WORLD EVIDENCE
- Fill evidence gap with large-scale, multi-stakeholder, post-marketing assessment of novel biologics and biosimilars
- Support the scientific community with methods development for research best practices in real-world evidence generation

EDUCATION
- Source of education for stakeholders

WHAT WE NEED:

ENGAGEMENT and SUPPORT!
- Manufacturers
- Pharmacy Benefit Managers
- Prescribers / Practitioners
- Patients
- Health Plans

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QUESTIONS?

Cate Lockhart, PharmD, PhD
Executive Director, BBCIC
clockhart@bbcic.org
Office: 703-684-2646