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Biologics and Biosimilars Collective Intelligence Consortium
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PRE-TEST
LQ1: Which of the following were barriers to generic drug adoption and utilization in the United States?

a. An unexpected side effect of the Hatch-Waxman Act that facilitated “pay-to-delay” arrangements
b. A 1988-1989 investigation resulted in convictions of FDA officials, manufacturers, and consultants for bribery
c. Patients and prescribers were uncomfortable with generic drugs
d. All of the above
LQ2: Which of the following is a LIMITATION of clinical trial data?

a. Designed to reduce confounding and bias
b. Potentially excludes large segments of the population who may be treated with the drug in real-world practice
c. Provides evidence that assesses safety and efficacy of the drug to support regulatory requirements
d. All of the above
LQ3: Data produced from research by organizations such as the Biologics and Biosimilars Collective Intelligence Consortium could be used to inform treatment and coverage decisions.

a. True
b. False
LQ4: There are multiple organizations conducting post-marketing surveillance specifically on biosimilars and their reference biologics in the United States

a. True
b. False
Outline

- It All Started With Generics
- Biosimilars: Definition and Regulatory Landscape
- Biosimilars: U.S. Market Access and Utilization
- Biosimilars: Data Sources for Decision-makers
- BBCIC: One Approach to Real-World Evidence Generation
- Sources of Post-Marketing Data
- Sources of Post-Marketing Data for BIOSIMILAR Research
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

ANDA
Market Exclusivity

GENERIC PRESCRIPTIONS (% of total)

- 1984: 33%
- 1989: 53%
- 2002: 72%
- 2008: 90%
- 2017: 90%

470 ANDAs filed

1069 ANDAs filed

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

Managers discovered to be **falsifying data**


Generic Drug Enforcement Act
Adverse Events

Hatch-Waxman Act

Meanwhile...

Generic Drugs

Market Exclusivity

“Pay-To-Delay”

1984
Economic Impact of Generics in the U.S.

- 90% of prescriptions filled with generics in 2017
- 23% of prescription drug spending attributed to generics
- $1.6 trillion in savings to the U.S. healthcare system in the past decade
- $265 billion in savings to the U.S. healthcare system in 2017 alone

https://accessiblemeds.org/resources/blog/2017-generic-drug-access-and-savings-us-report
https://accessiblemeds.org/resources/blog/2016-generic-drug-access-and-savings-report
Biosimilars: Definition and Regulatory Landscape
Types of Drugs: Chemical vs Biologic

**Chemical Drugs**
- Well-defined composition
- Simple structure
- Small size
- Minimal or no heterogeneity
- Typically have more than one pharmacological target

**Biologic Drugs**
- Composition defined to a certain extent
- Complex structure
- Big size
- Significant (micro) heterogeneity
- Often highly specific

Original | Generic
---|---

Original | Biosimilar
Definitions

Biosimilar or Biosimilarity

“the biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components” and “there are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity, and potency of the product” [PHS Act Section 351(i)(2)]

Reference Product

“the single biological product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k)” [PHS Act Section 351(i)(4)]
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

2010

351(k) Application

www.fda.gov/biosimilars
Requirements for FDA Registration

Compared to Reference Product:

- Biosimilar*
- Mechanism of action
- Label Indications
- Dosage form/Route/Strength
- Manufacturing

https://www.fda.gov/biosimilars
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

https://www.fda.gov/biosimilars
## Development of Original, Generic and Biosimilar Medicines

### Development of a novel drug (chemical or biological)

<table>
<thead>
<tr>
<th>Molecular generators</th>
<th>In vitro tests and preclinical studies in animals</th>
<th>Phase I trial</th>
<th>Phase II trial</th>
<th>Phase III trial</th>
</tr>
</thead>
</table>

### Development of a generic medicine

<table>
<thead>
<tr>
<th>Molecular generators</th>
<th>Quality, purity and stability assays</th>
<th>BE copy</th>
</tr>
</thead>
</table>

### Development of a biosimilar biological drug

<table>
<thead>
<tr>
<th>Molecule generation</th>
<th>Molecular characterization and in vitro biosimilarity demonstration</th>
<th>Preclinical assay in animals</th>
<th>Phase I trial</th>
<th>Phase II trial</th>
</tr>
</thead>
</table>

**Comparability exercise**

- Essential demonstration of biosimilarity
- Security and activity confirmation

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Biosimilars in Development in the U.S.

NUMBER of PRODUCTS in FDA’s BIOSIMILAR DEVELOPMENT PROGRAM

- 2013: 29
- 2014: 46
- 2015: 56
- 2016: 62
- 2017: 65
Biosimilars Approved in US – as of September 2018

- **2015**
  - filgrastim-sndz (Zarxio®)
  - insulin glargine (Basaglar®)*

- **2016**
  - infliximab-dyyb (Inflectra®)
  - etanercept-szzs (Erelzi™)
  - adalimumab-atto (Amjevita™)

- **2017**
  - adalimumab-abdm (Cyltezo™)
  - bevacizumab-awwb (Mvasi™)
  - trastuzumab-dkst (Ogivri™)
  - insulin lispro (Admelog®)*
  - infliximab-qbtx (Ixifi™)

- **2018**
  - epoetin alfa-epbx (Retacrit™)
  - pegfilgrastim-jmdb (Fulphila™)
  - filgrastim-aafi (Nivestym™)

*FDA approval as a follow-on biologic


# Biosimilars Approved by EMA – as of September, 2018

<table>
<thead>
<tr>
<th>Year of EMA Approval</th>
<th>Biosimilar Product</th>
<th>Reference Product</th>
<th>Number of Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>Somatropin</td>
<td>Norditropin®</td>
<td>2</td>
</tr>
<tr>
<td>2007</td>
<td>Epoetin alfa</td>
<td>Epogen®</td>
<td>3</td>
</tr>
<tr>
<td>2007</td>
<td>Epoetin zeta</td>
<td>Retacrit®</td>
<td>2</td>
</tr>
<tr>
<td>2013/2014</td>
<td>Follitropin alfa</td>
<td>Gonal-f®</td>
<td>2</td>
</tr>
<tr>
<td>2013/2016/2018</td>
<td>Infliximab</td>
<td>Remicade®</td>
<td>4</td>
</tr>
<tr>
<td>2014/2017/2018</td>
<td>Insulin glargine</td>
<td>Lantus®</td>
<td>3</td>
</tr>
<tr>
<td>2016</td>
<td>Enoxaparin sodium</td>
<td>Lovenox®</td>
<td>2</td>
</tr>
<tr>
<td>2016/2017</td>
<td>Etanercept</td>
<td>Enbrel®</td>
<td>2</td>
</tr>
<tr>
<td>2017/2018</td>
<td>Adalimumab</td>
<td>Humira®</td>
<td>8</td>
</tr>
<tr>
<td>2017</td>
<td>Insulin lispro</td>
<td>Humalog®</td>
<td>1</td>
</tr>
<tr>
<td>2017</td>
<td>Rituximab</td>
<td>Rituxan®</td>
<td>6</td>
</tr>
<tr>
<td>2017</td>
<td>Teriparatide</td>
<td>Forteo®</td>
<td>2</td>
</tr>
<tr>
<td>2017/2018</td>
<td>Trastuzumab</td>
<td>Herceptin®</td>
<td>4</td>
</tr>
<tr>
<td>2018</td>
<td>Bevacizumab</td>
<td>Avastin®</td>
<td>1</td>
</tr>
<tr>
<td>2018</td>
<td>Pegfilgrastim</td>
<td>Neulasta®</td>
<td>2</td>
</tr>
</tbody>
</table>

**TOTAL APPROVALS = 53**

*3 were withdrawn in 2011, 2012, and 2016*
Biosimilars:
U.S. Market Access and Utilization
Current Utilization Patterns in the U.S.

2017

filgrastim-sndz (Zarxio®) → 22% of filgrastim sales

infliximab-dyyb (Inflectra®) → 1.6% of infliximab sales

Biosimilar Sales

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

- United States:
  - Biologic Sales: 59%
  - Biosimilar Sales: 2%

- Europe:
  - Biologic Sales: 22%
  - Biosimilar Sales: 87%

- Japan:
  - Biologic Sales: 6%
  - Biosimilar Sales: 13%

- Other:
  - Biologic Sales: 7%
  - Biosimilar Sales: 4%

Factors Influencing U.S. Biosimilar Utilization

1. Regulatory
2. Business Decisions
3. Uncertainty
Factors Influencing U.S. Biosimilar Utilization

1. Regulatory

2. Business Decisions

3. Uncertainty
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 payers; and

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

Factors Influencing U.S. Biosimilar Utilization

1. Regulatory
2. Business Decisions
3. Uncertainty
Factors Influencing U.S. Biosimilar Utilization

- BPCIA
- Market Tactics
  - "Pay-To-Delay"
  - Contracting
  - Patent Litigation

2010

Factors Influencing U.S. Biosimilar Utilization

1. Regulatory
2. Business Decisions
3. Uncertainty
**Factors Influencing U.S. Biosimilar Utilization**

**Uncertainty - 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....

<table>
<thead>
<tr>
<th>Specialty Physician</th>
<th>Agree Biosimilars are Safe and Appropriate for Naïve and Existing Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>44.8%</td>
</tr>
<tr>
<td>Rheumatology</td>
<td>34.5%</td>
</tr>
<tr>
<td>Dermatology</td>
<td>37.5%</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>43.8%</td>
</tr>
<tr>
<td>Nephrology</td>
<td>45.5%</td>
</tr>
<tr>
<td>Medical Oncology</td>
<td>50.5%</td>
</tr>
<tr>
<td>Hematology-Oncology</td>
<td>57.0%</td>
</tr>
</tbody>
</table>
### Factors Influencing U.S. Biosimilar Utilization

#### Uncertainty - Patients


<table>
<thead>
<tr>
<th></th>
<th>Biologics</th>
<th>Biosimilars</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basic awareness</td>
<td>No knowledge</td>
</tr>
<tr>
<td>Patient (n=635)</td>
<td>30%</td>
<td>33%</td>
</tr>
<tr>
<td>Patient advocate (n=245)</td>
<td>47%</td>
<td>10%</td>
</tr>
<tr>
<td>General public (n=250)</td>
<td>11%</td>
<td>57%</td>
</tr>
</tbody>
</table>

- Basic awareness = Defined as reporting at least a general impression of biologics or knew the term “biologic” or “biosimilars”.
- **N = 3,198** patients with inflammatory diseases or cancer that could be treated with available biosimilars.
- 38.8% from US.

Note: “Caregiver” category (N = 111) not included in this table
Not all categories sum to 100% due to rounding.
Factors Influencing U.S. Biosimilar Utilization

Uncertainty - Patients


- Basic awareness: Defined as reporting at least a general impression of biologics or knew the term “biologic” or “biosimilars”.

**Percent of U.S. Patients Who Agree with Each Statement**

<table>
<thead>
<tr>
<th>Statement</th>
<th>Unaware of Biosimilars (n = 610)</th>
<th>Aware of Biosimilars (n = 270)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective care/Reasonable cost</td>
<td>24%</td>
<td>40%</td>
</tr>
<tr>
<td>Affordable</td>
<td>19%</td>
<td>37%</td>
</tr>
<tr>
<td>Effective treatment</td>
<td>21%</td>
<td>33%</td>
</tr>
<tr>
<td>Best option</td>
<td>21%</td>
<td>41%</td>
</tr>
<tr>
<td>Has minimal side effects</td>
<td>21%</td>
<td>34%</td>
</tr>
<tr>
<td>Is safe</td>
<td></td>
<td>47%</td>
</tr>
<tr>
<td>Comfortable switching</td>
<td></td>
<td>51%</td>
</tr>
</tbody>
</table>

Basic awareness = Defined as reporting at least a general impression of biologics or knew the term “biologic” or “biosimilars”.
Factors Influencing U.S. Biosimilar Utilization

Post-approval studies evaluating comparative safety and effectiveness will be critical to generating real-world evidence to inform clinical practices and policy decisions.

Medical Specialists’ Attitudes to Prescribing Biosimilars

Subjective Complaints as the Main Reason for Biosimilar Discontinuation After Open-Label Transition from Reference Infliximab to Biosimilar Infliximab
*Arthritis Rheumatol* 2018;70(1):60-68.

Barsell et al. A Survey Assessment of US Dermatologists’ Perception of Biosimilars
*J Drugs Dermatol* 2017;16(6):6122-615.

....and others

OPPORTUNITY FOR EDUCATION
Biosimilars: Data Sources for Decision-Makers
Data Source – Clinical Trials

Strengths:

Randomized Controlled Trials (RCTs) = **GOLD STANDARD**

Carefully designed to reduce:

- BIAS
- CONFOUNDING
- PLACEBO EFFECT

Limitations:

- May not be sufficient to address all relevant questions
- Exclude potentially large segments of the population
- Cover a limited length of time, often very short
- Do not often reflect normal clinical settings
- Very Expensive

Real world evidence development initiatives are focused on expanding evidence *effectively, rapidly and cost effectively* (e.g., FDA EvGen, PCORI, NIH Collaboratory).

**Origins in the Gap in Evidence**

Real-world utilization quickly outpaces available clinical evidence.

**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

**Phase 1**
- 20-100 healthy volunteers

**Phase 2**
- 100-500 patients with target condition

**Phase 3**
- 1000-5000 patients with target condition

**Phase 4**
- Post-marketing research and monitoring

**6-7 years & $0.8B-$1.2B on a few thousand patients**
Data Sources – Real World Evidence (RWE)

“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.

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.
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
- Data provide rich source of information for patient safety evaluations

Commonly Used Data Sources
- Administrative Claims
- Electronic Medical Records

Demographic

<table>
<thead>
<tr>
<th>Coverage</th>
<th>PatID</th>
<th>Birth Date</th>
<th>Sex/Race</th>
<th>ZIP Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvard Pilgrim HealthCare</td>
<td>5291321</td>
<td>07/29/63</td>
<td>M/Unknown</td>
<td>02119</td>
</tr>
</tbody>
</table>

Lives in Boston, MA

Has appendectomy

Diagnosed with hypertension

Routine Office Visit

Bob’s Story

Bob is a 47-50 year old male with 1,035 days of observed time.

Encounter
- 1/1/2011 Office Visit
  - Dx: Influenza with pneumonia
- 3/15/2012 Emergency Department
  - Px: appendectomy
  - 3/15/2012-3/18/2012 Hospital Inpatient stay
- 12/11/12 Office Visit
  - Dx: Hypertension
  - Rx: Anti-hypertensive
- 1/1/2011 Rx: Antibiotic
- 1/1/2011 Rx: Antibiotic
- 10/31/13 Office Visit
  - Dx: Hypertension
- 3/15/2012 Rx: Antibiotic

Dispensings
- 1/1/2011 Rx: Antibiotic
- 1/1/2011 Rx: Antibiotic
- 10/31/13 Rx: Antibiotic

Encounters

2011

2012

2013

2014
ISPOR/ISPE Task Force on RWE - Recommendations

- Define study (questions and purpose)
  - Exploratory
  - Hypothesis evaluating treatment effectiveness (HETE)
- Public posting of study protocol and analysis plan
- Publish study results (or post on website)
- Enable replication (same data and analyses)
- Confirm important findings (2nd data source & population)
- Publicly address methodologic criticism after publication
- Include key stakeholders in design, conduct & dissemination

Berger et al. Value in Health 2017;20:1001-8
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

BBCIC: One Approach to Real-World Evidence Generation
A non-profit, multi-stakeholder, scientific public service initiative conducting rigorous post-marketing observational research to monitor biosimilar products and novel biologics for effectiveness and safety.
BBCIC Purpose: Why the BBCIC Is Needed

Generics saved the US well over $1.6 trillion in past decade but it took 20 years.

- Generics are safe and effective, resulting in increased patient access to critical medications.
- Slow generic uptake influenced by anecdotal reports that got wide press coverage.
- Lingering uncertainty among physicians and patients about safety and comparability.

Physician survey, 2011

23% – concern about efficacy
50% – concern about quality

Physician survey, 2015

78% – very concerned about safety/immunogenicity

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 ~150 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
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 Partner Organizations

Coordinating Center

Harvard Pilgrim Health Care Institute

Data and scientific partners

HealthCore
Anthem
Kaiser Permanente Washington Health Research Institute
Harvard Pilgrim Health Care
HOPA Hematology/Oncology Pharmacy Association
Aetna
Express Scripts
Optum
Health Care Systems Research Network HealthPartners, Henry Ford Health System

Convened by

AMCP Academy of Managed Care Pharmacy®
BBCIC Scientific Operations

- Disease and Biologic Products (Research Teams)
- Descriptive Studies
- Hypothesis-driven Comparative Safety and Effectiveness Studies
- Data & Infrastructure
- Study Design & Analytic Methods (Work Groups)
- Data Availability & Characterization
- Study Design & Methods

Gaps
Solutions
Strengths of BBCIC

- **Stakeholders** play an active and extensive role
- **Focus** on biologic class and diseases for new biosimilars

**Descriptive analysis**
- To understand patients, disease, treatments, outcomes
- To understand data, methods, gaps, possible solutions

**Comparative analysis**
- Both safety and effectiveness
- All biosimilars for originator biologic

- **Active surveillance**
- **Leverage Sentinel**
BBCIC Progress to Date

- **June 2015**: Consortium officially kicked off
- **October 2015**: Governance approved
- **February 2016**: First research plan approved
- **Q3 2016**: Three research protocols initially registered on http://www.clinicaltrials.gov
- **Four research teams convened**
- **Q3 2017**: Descriptive analyses conclude
- **Q4 2017**: Switching and NDC/J-Code Workgroups convened
- **Q1 2018**: Descriptive analysis publications in preparation
- **Q1 2018**: CER Methods and ICD-10 Conversion Workgroups convened
- **Q4 2018**: Convene CER Research, Trastuzumab descriptive analysis, Switching Methods descriptive analysis
BBCIC 2017-2019: Lines of inquiry

- 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**
BBCIC - Progress

- What we have DONE
- What we are DOING
- What we PLAN to DO
## Descriptive Analysis Research Teams

In 2016, the BBCIC Science Committee convened 4 research teams to conduct descriptive analyses using the BBCIC DRN.

<table>
<thead>
<tr>
<th>Project</th>
<th>Disease Indications</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Insulins</strong></td>
<td>• Diabetes</td>
<td>Insulin</td>
</tr>
<tr>
<td><strong>Colony Stimulating Factors</strong></td>
<td>• Febrile Neutropenia risk reduction in non-myeloid malignancies treated with myelosuppressive anti-cancer drugs associated with febrile neutropenia</td>
<td>Filgrastim (Neupogen), PEG-filgrastim (Neulasta), TBO-filgrastim, filgrastim-sndz (Zarxio)</td>
</tr>
<tr>
<td>(G-CSF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Anti-Inflammatories</strong></td>
<td>• Rheumatoid Arthritis • Psoriasis • Psoriatic Arthritis • Ankylosing Spondylitis • Ulcerative Colitis • Crohn's Disease</td>
<td>Adalimumab (Humira), infliximab (Remicade), infliximab-dyyb (Inflectra), infliximab-abda (Renflexxis), rituximab (Rituxan), tocilizumab (Actemra), abatacept (Orencia), etanercept (Enbrel), certolizumab (Cimzia), golimumab (Simponi), ustekinumab (Stelara), secukinumab (Cosentyx), natalizumab (Tysabri), golimumab (Simponi)</td>
</tr>
<tr>
<td><strong>Erythropoetin-Stimulating Agents (ESA)</strong></td>
<td>• Anemia (CKD, Hemodialysis)</td>
<td>Epoetin alfa (Epogen, Procrit) darbepoetin alfa (Aranesp), methoxy polyethylene glycol-epoetin beta (Miracea)</td>
</tr>
</tbody>
</table>
Descriptive Analysis Research Teams

In 2016, the BBCIC Science Committee convened 4 research teams to conduct descriptive analyses using the BBCIC DRN

<table>
<thead>
<tr>
<th>Project</th>
<th>Objective</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulins</td>
<td>Describe treatment patterns and outcomes of adult patients with diabetes who use long-acting (LAI) or intermediate-acting (NPH) insulin</td>
<td>(1) major cardiac events, combined; severe hypoglycemic events; (2) A1C baseline and follow-up</td>
</tr>
<tr>
<td>Colony Stimulating Factors (G-CSF)</td>
<td>Descriptive analysis G-CSF use in breast or lung cancer patients who received chemotherapy with Grade III or IV neutropenic-risk.</td>
<td>(1) rate of hospitalizations; (2) severe neutropenia; anaphylaxis; combined measure of bone pain, glomerulonephritis, capillary leak syndrome, hyperleukocytosis and splenic rupture.</td>
</tr>
<tr>
<td>Anti-Inflammatories</td>
<td>Describe treatment patterns and outcomes of patients with autoimmune diseases receiving biologic treatments</td>
<td>Serious infections requiring hospitalization.</td>
</tr>
<tr>
<td>Erythropoeitin-Stimulating Agents (ESA)</td>
<td>Assess the feasibility of currently available BBCIC data to conduct a study of ESA biosimilars and innovators in hemodialysis (HD) patients.</td>
<td>Chronicity of HD among patients; similarity of population of HD patients described by USRDS</td>
</tr>
</tbody>
</table>

- 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.
### Descriptive Analysis – Lessons Learned

**OVERALL:**
- The BBCIC DRN is robust and reliable for large-scale observational studies
- Additional methods and data sources are being incorporated to enrich the data and capabilities of the BBCIC

<table>
<thead>
<tr>
<th>Project</th>
<th>Challenges</th>
<th>Lessons Learned/Solutions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulins</td>
<td>• Design Considerations</td>
<td>• Coding algorithms for diagnosis inconsistency</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Careful attention to episode gap length</td>
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<tr>
<td></td>
<td></td>
<td>• Alternative methods for patient adherence</td>
</tr>
<tr>
<td>G-CSF</td>
<td>• Exposures • Outcomes</td>
<td>• Broader inclusion criteria</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Careful attention to covariates and clinical outcome measures</td>
</tr>
<tr>
<td>Anti-Inflammatory</td>
<td>• Outcomes</td>
<td>• Clinical effectiveness measures are difficult to identify from administrative claims</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Pilot to link PRO and clinical measures to claims</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Include linked EMR + claims data sources</td>
</tr>
<tr>
<td>ESA</td>
<td>• Data Sources</td>
<td>• Data sources with adequate patient numbers</td>
</tr>
</tbody>
</table>
BBCIC - Progress

• What we have **DONE**

• What we are **DOING**

• What we **PLAN** to **DO**
Lessons Learned - Infrastructure Improvements

**Data Improvements**
- Address multiple gaps identified in descriptive analyses
- Pilots with Patient Reported Outcomes from MTM or Specialty Pharmacy providers
- Pilots with mobile health patient reported outcomes tied longitudinally to the Common Data Model

**Add Data Partners**
- Cancer Research Network
- Medicare ESRD Full data set
- Anthem HealthCore Integrated Research Environment (HIRE)
- ASCO CancerLinQ

**Expand Common Data Model**
- Outcomes measures
Workgroups

In 2017, the BBCIC Science Committee convened 4 workgroups to develop best practices in research methodology and a platform for future studies.

<table>
<thead>
<tr>
<th>Project</th>
<th>Challenges Addressed</th>
<th>Study Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switching</td>
<td>• Design Considerations</td>
<td>Treatment of switching/sequencing as a covariate/confounder in BBCIC CER studies</td>
</tr>
<tr>
<td>CER Methods</td>
<td>• Design Considerations</td>
<td>Develop best-practices based on current methodology for conducting observational comparative-effectiveness research</td>
</tr>
<tr>
<td>NDC / J-Code</td>
<td>• Exposures • Outcomes</td>
<td>Investigate the extent to which NDCs are being supplied on physician-office claims</td>
</tr>
<tr>
<td>ICD-10 Mapping</td>
<td>• Exposures • Outcomes</td>
<td>In preparation for future descriptive and CER projects, ICD-9 codes are being mapped to ICD-10 codes to allow utilization of data both before and after October 2015.</td>
</tr>
</tbody>
</table>
BBCIC - Progress

• What we have **DONE**
• What we are **DOING**
• What we **PLAN to DO**
Upcoming BBCIC Research - 2019

**COMPARATIVE EFFECTIVENESS**

**G-CSF**
First BBCIC CER study to compare the G-CSF originator biologic to available biosimilars in the US. The Research Team is expected to kickoff in Q4 of 2018 and research will commence in earnest by the end of the year.

**Insulins**
The topic of a PCORI grant application.

**DESCRIPTIVE ANALYSIS**

**Trastuzumab Descriptive Analysis**
We anticipate research will commence research in Q1 2019.

**METHODS**

**Switching Methods Descriptive Analysis**
The next phase of the Switching Methods Workgroup. This study will include an in-depth discussion of best practices for study design, and a descriptive analysis to test study designs in the BBCIC DRN.
Expanded Research Scope
• Priority research in current and emerging BIOSIMILARS
• We are the BIOLOGICS and Biosimilars Collective Intelligence Consortium
• Opportunities for drug class or disease level research

Expanded Partnerships
• Pursuing partnerships to leverage resources for specific projects
• Seeking new participating members (manufacturers, managed care, PBMs, research organizations, data partners)

Expanded Data Capabilities
• Adding new data sources to enrich the BBCIC DRN
• Exploring inclusion of patient-reported and clinical data with administrative claims

Expanded Communications Plan
• PUBLICATIONS!!
• Increased public exposure to research programs and results
Anticipated Publications in 2019

- **Methods and Infrastructure**
  - CER Methods Systematic Review
  - CER Methods Best-Practices and Recommendations
  - ICD-9 to ICD-10 Mapping
  - NDC/J-Code Patterns and Implications in Physician Claims
  - Switching Patterns Descriptive Analysis

- **Observational Research**
  - Descriptive Analyses: Insulins, Anti-Inflammatories, G-CSF, ESA
  - G-CSF: Design of a CER Study
  - G-CSF: Preliminary Results
  - Trastuzumab: Design of a Descriptive Analysis
  - Trastuzumab: Preliminary Results
Practical Application of BBCIC Research

**WHAT WE PROVIDE:**

**REAL-WORLD EVIDENCE**
Fill *evidence gap* with large-scale, multi-stakeholder, post-marketing assessment of biosimilars and reference biologics

**EDUCATION**
Source of *education* for stakeholders

**WHAT WE NEED:**

**ENGAGEMENT**
- Health Plans
- Pharmacy Benefit Managers
- Patients
- Prescribers and Healthcare Practitioners
- Manufacturers
Sources of Post-Marketing Data
Rapidly Evolving Landscape

- FDA (U.S. Food and Drug Administration)
  - [https://fda.gov](https://fda.gov)

- EvGen (Evidence Generation)

- Sentinel Initiative

- Innovation in Medical Evidence Development and Surveillance

- Reagan-Udall Foundation for the Food and Drug Administration

- CNODES (Canadian Network for Observational Drug Effect Studies)
  - [https://www.cnodes.ca](https://www.cnodes.ca)

- pcornet (The National Patient-Centered Clinical Research Network)
  - [https://pcornet.org](https://pcornet.org)
Sources of Post-Marketing Data for BIOSIMILAR Research
To date the only multi-stakeholder, multi-source research consortium dedicated to proactive surveillance of safety and effectiveness of **biosimilar products and reference biologics** in the United States.
POST-TEST
LQ1: Which of the following were barriers to generic drug adoption and utilization in the United States?

a. An unexpected side effect of the Hatch-Waxman Act that facilitated “pay-to-delay” arrangements
b. A 1988-1989 investigation resulted in convictions of FDA officials, manufacturers, and consultants for bribery
c. Patients and prescribers were uncomfortable with generic drugs
d. All of the above
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LQ2: Which of the following is a LIMITATION of clinical trial data?

a. Designed to reduce confounding and bias
b. Potentially excludes large segments of the population who may be treated with the drug in real-world practice
c. Provides evidence that assesses safety and efficacy of the drug to support regulatory requirements
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d. All of the above
LQ3: Data produced from research by organizations such as the Biologics and Biosimilars Collective Intelligence Consortium could be used to inform treatment and coverage decisions.

a. True
b. False
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a. True
b. False
LQ4: There are multiple organizations conducting post-marketing surveillance specifically on biosimilars and their reference biologics in the United States

a. True
b. False
LQ4: There are multiple organizations conducting post-marketing surveillance specifically on biosimilars and their reference biologics in the United States

a. True
b. False
QUESTIONS?

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