BBCIC
Biologics & Biosimilars
Collective Intelligence Consortium
AMCP BBCIC, LLC

Real-World Evidence and Post-Marketing Surveillance to Support Treatment and Coverage Decisions

Cate Lockhart, MS, PharmD, PhD
Executive Director, BBCIC
January 23, 2019

Outline

- It All Started with Generics
- Then Came Biosimilars
- Barriers to Biosimilars
- Data Sources for Decision Makers
- BBCIC: One Approach to Real-World Evidence

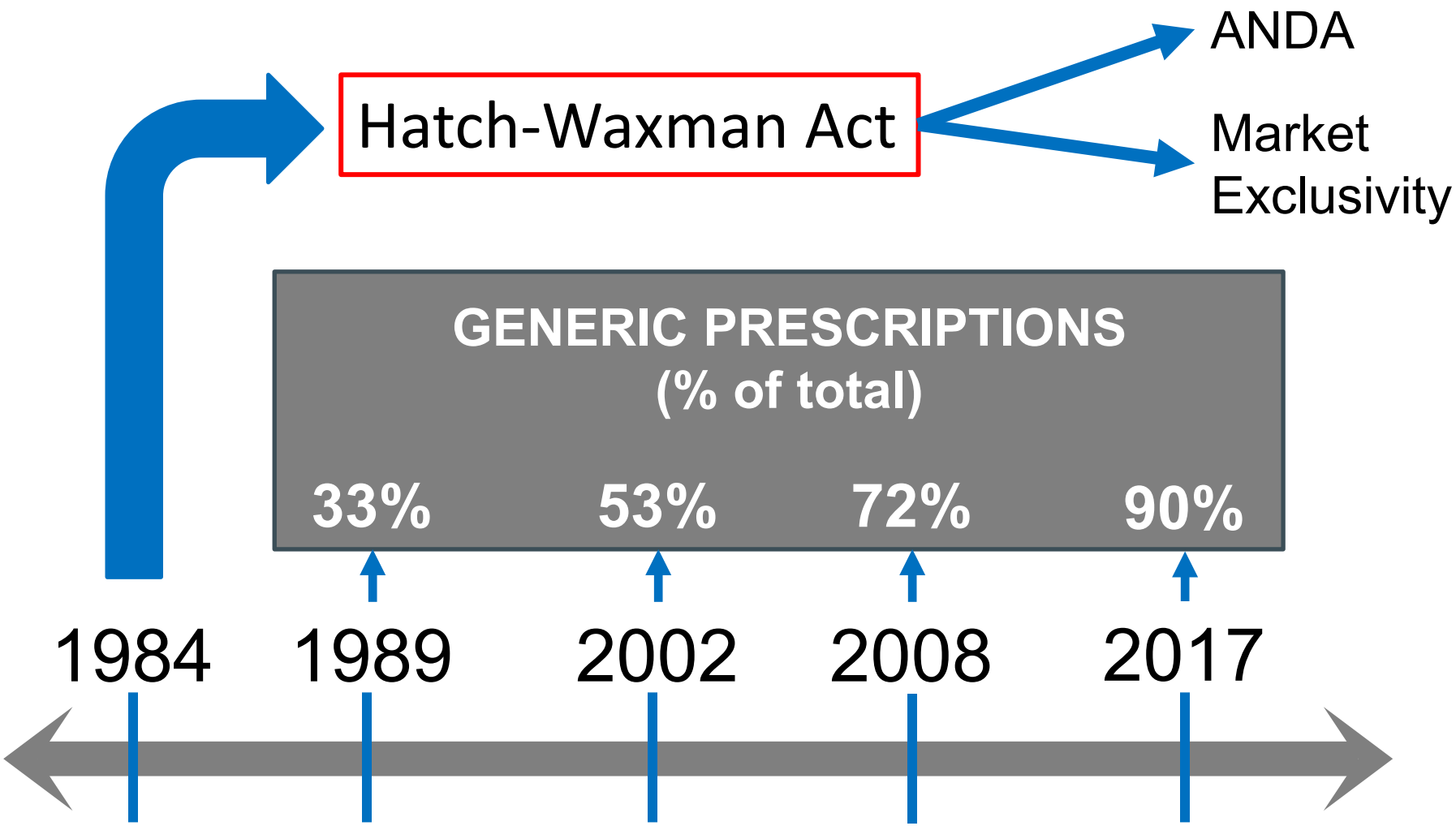
It All Started With Generics

History of Generic Drugs in the U.S.

1984

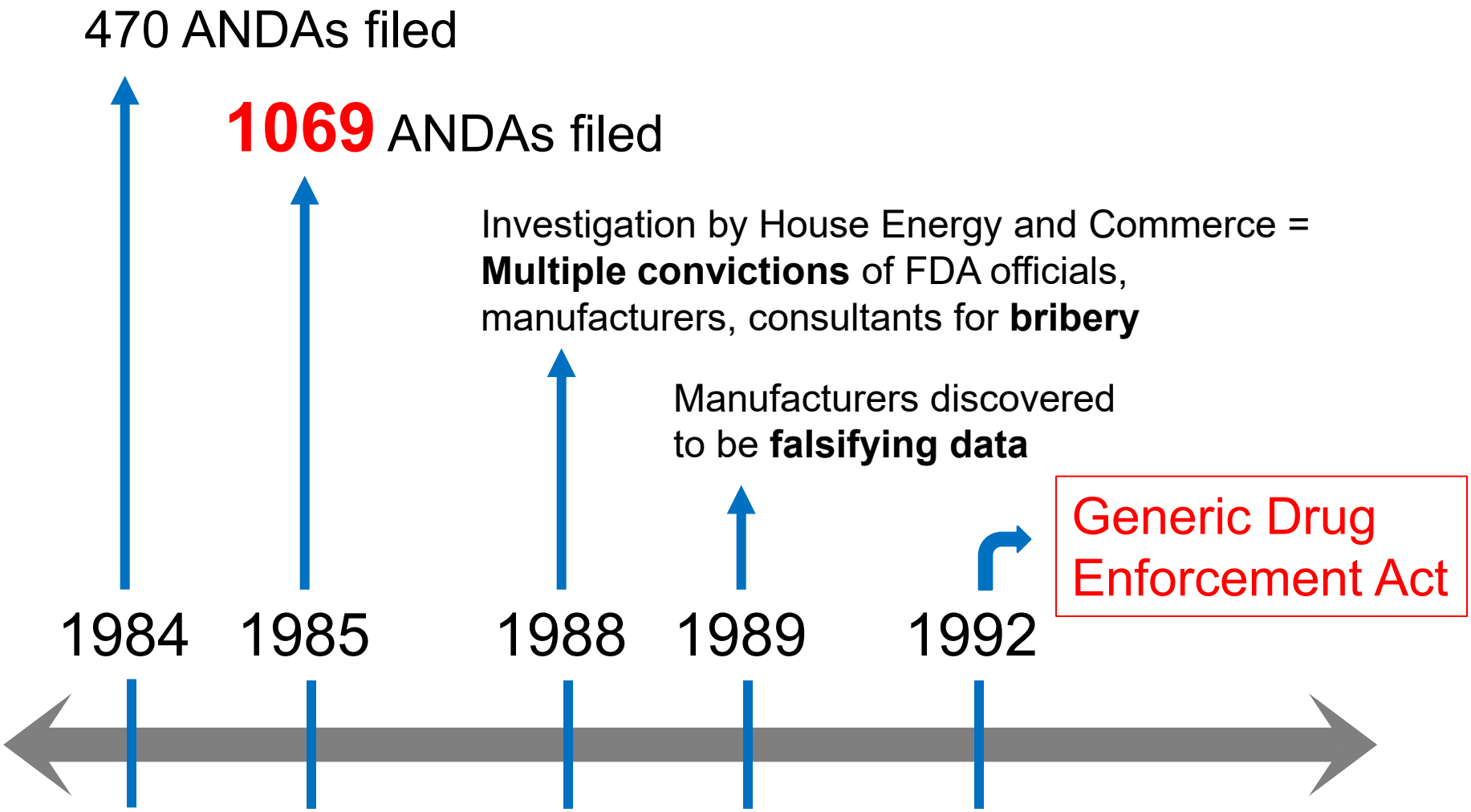
Lewis, et al. *J Contemporary Health Law & Policy*. 1992;8(1):361-378.
Boehm, et al. *Acta Pharmaceutica Sinica B*. 2013;3(5):297-311.

History of Generic Drugs in the U.S.



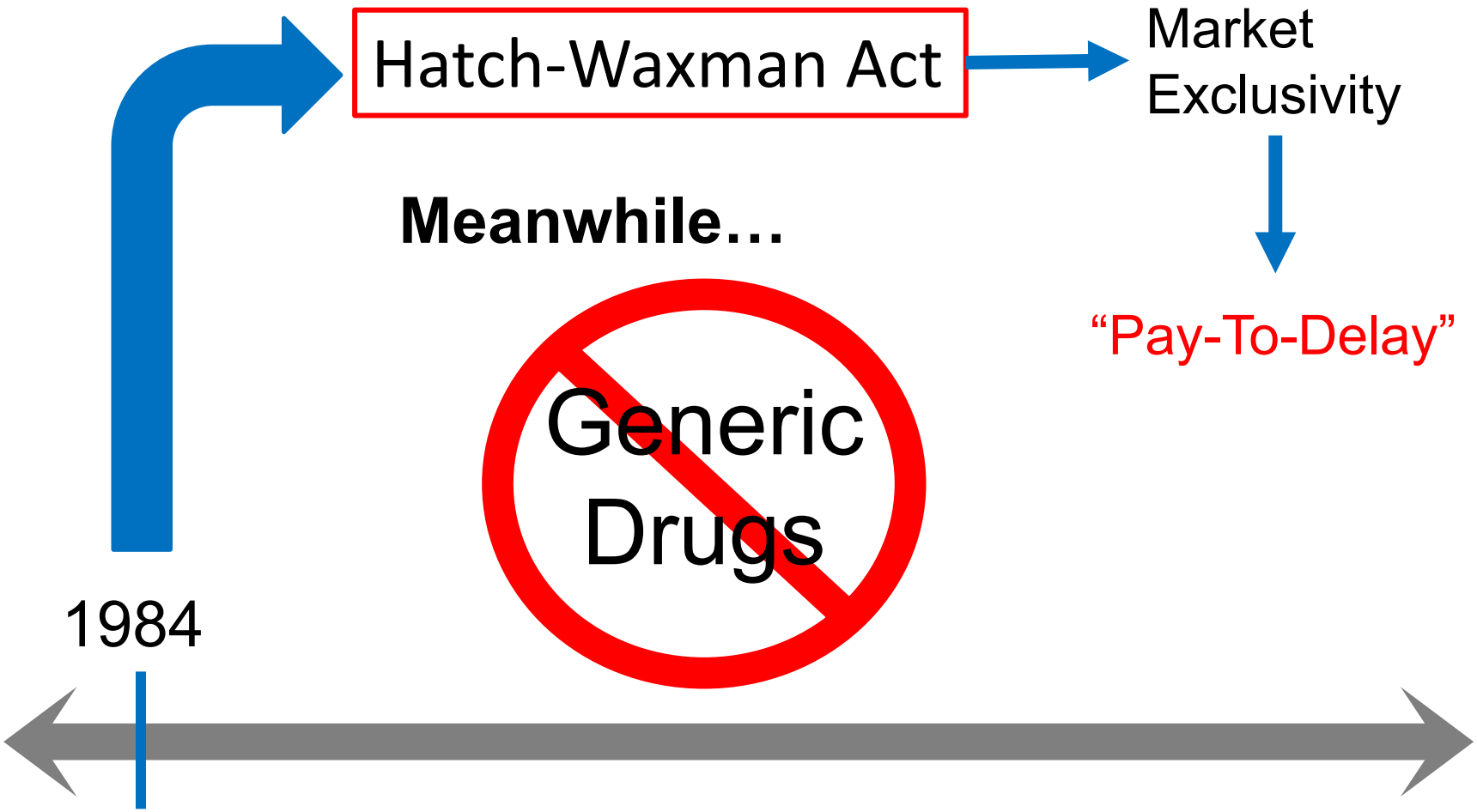
Lewis, et al. *J Contemporary Health Law & Policy*. 1992;8(1):361-378.
Boehm, et al. *Acta Pharmaceutica Sinica B*. 2013;3(5):297-311.
Thayer. *Chemical & Engineering News*. 2014;92(39):8-16.

Adverse Events



Lewis, et al. *J Contemporary Health Law & Policy*. 1992;8(1):361-378.
Kesselheim AS. CMAJ 2011;183(12):1350-1351.
Eban K. *Self* 2009. www.self.com /health/2009/06/dangers-of-generic-drugs?currentPage=1.
Huckman M. CNBC. 2007 Oct. 29. Available: www.cnbc.com/id/21528009.

Adverse Events



Lewis, et al. *J Contemporary Health Law & Policy*. 1992;8(1):361-378.
Kesselheim AS. CMAJ 2011;183(12):1350-1351.
Eban K. *Self* 2009. www.self.com /health/2009/06/dangers-of-generic-drugs?currentPage=1.
Huckman M. CNBC. 2007 Oct. 29. Available: www.cnbc.com/id/21528009.

Economic Impact of Generics in the U.S.

90% Prescriptions **filled** with **generics** in 2017

23% Prescription drug **spending** attributed to **generics**

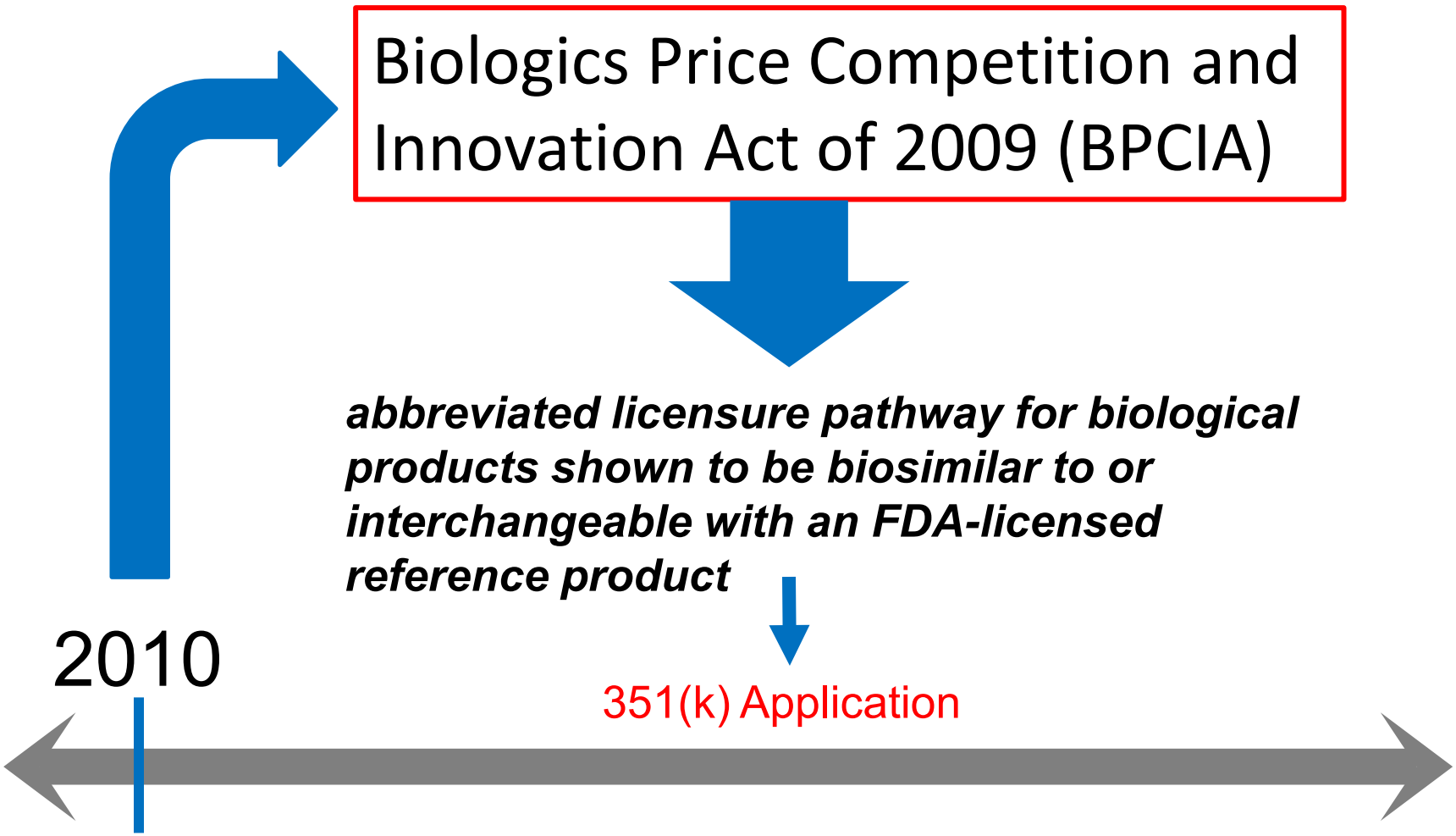
$1.6 trillion Savings to U.S. healthcare system in the past **decade**

$265 billion Savings to the U.S. healthcare system in **2017 alone**

https://accessiblemeds.org/resources/blog/2018-generic-drug-access-and-savings-report
https://accessiblemeds.org/resources/blog/2017-generic-drug-access-and-savings-us-report
https://accessiblemeds.org/resources/blog/2018-generic-drug-access-and-savings-report

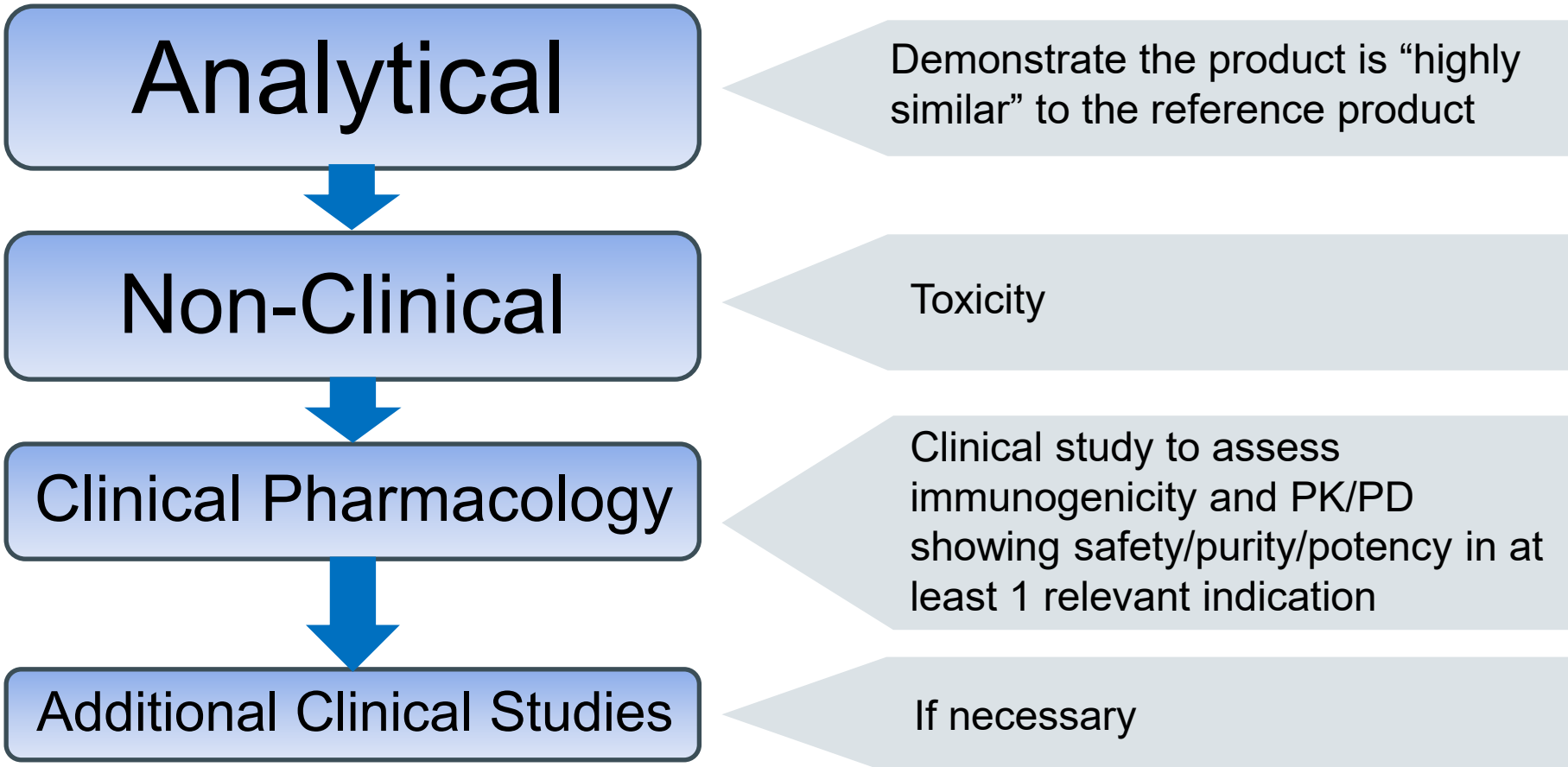
Then Came Biosimilars…

Biosimilars in the U.S.

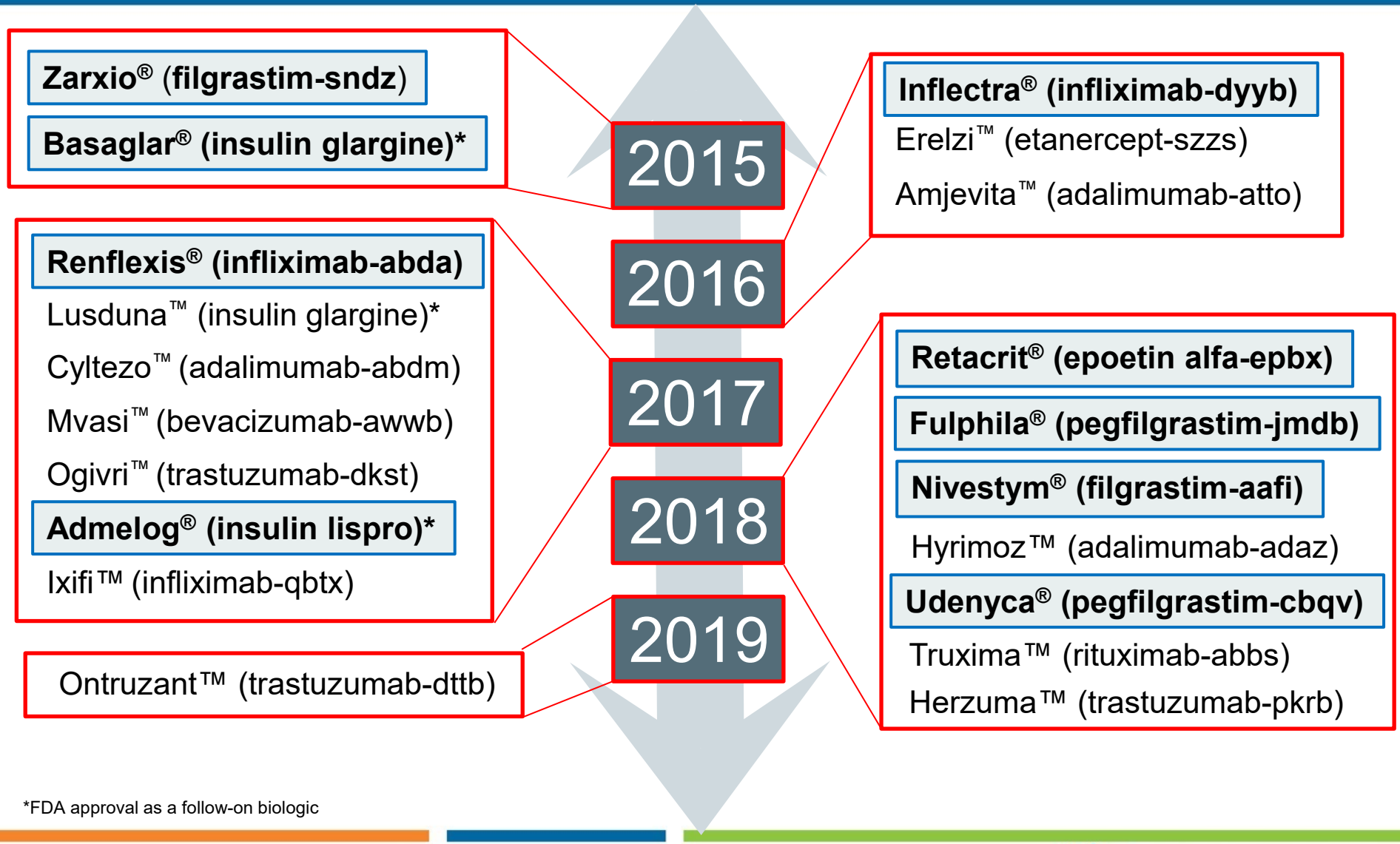


Requirements for FDA Registration

Demonstrating Biosimilarity → TOTALITY of EVIDENCE



Biosimilars Approved in US – as of January 2019



*FDA approval as a follow-on biologic

Biosimilars Review & Report. https://biosimilarsrr.com/us-biosimilar-filings/ (accessed September 5, 2018)
US Food and Drug Administration CDER List of Licensed Biological Products http://www.fda.gov (accessed September 5, 2018)

Biosimilars Approved by EMA – as of December 2018

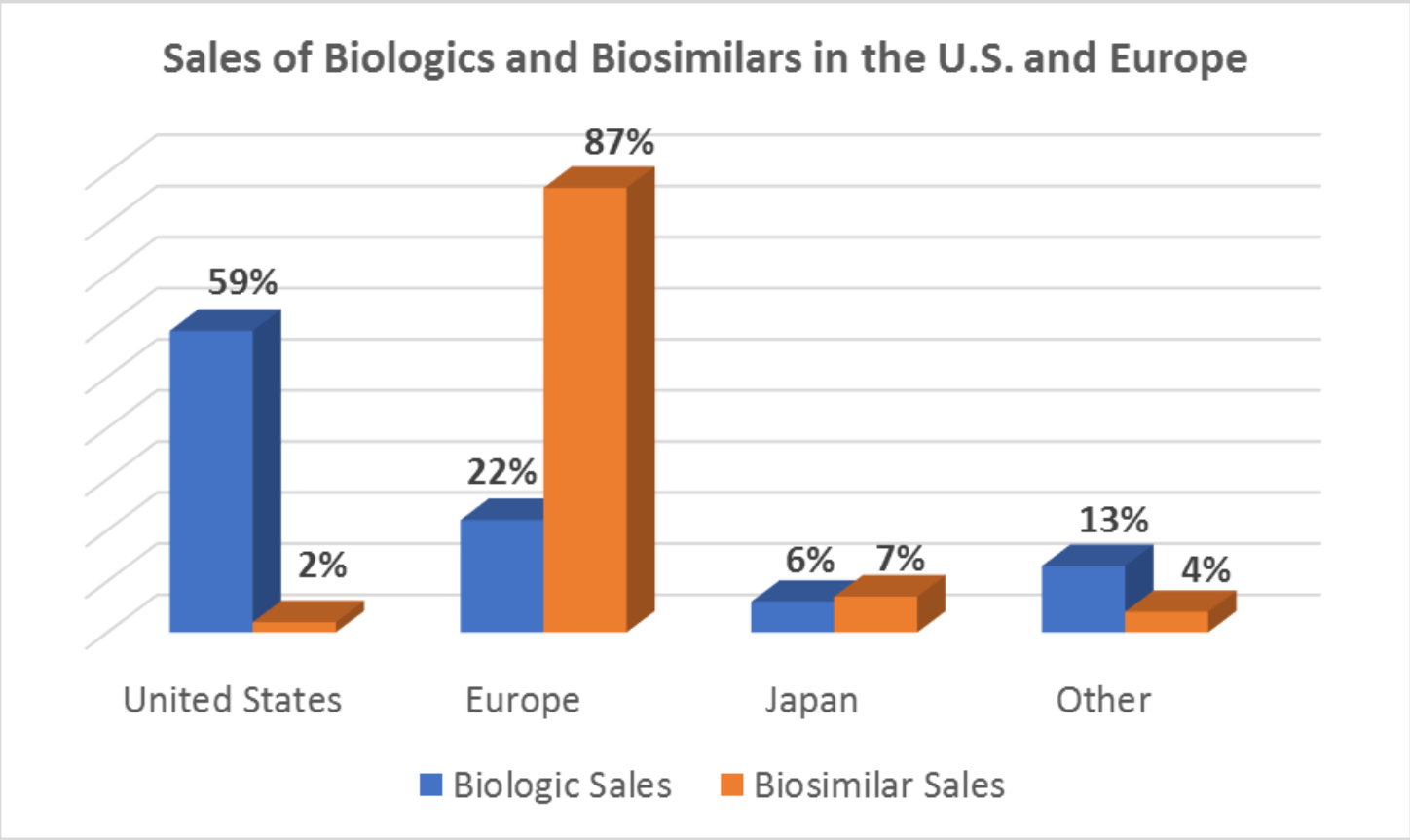
Year of EMA Approval	Biosimilar Product	Reference Product	Number of Products
2006	Somatropin*	Norditropin®	3
2007	Epoetin alfa	Epogen®	3
2007	Epoetin zeta	Retacrit®	2
2008/2009/2010/2013/2014	Filgrastim*	Neupogen®	9
2013/2014	Follitropin alfa	Gonal-f®	2
2013/2016/2018	Infliximab	Remidade®	4
2014/2017/2018	Insulin glargine	Lantus®	3
2016	Enoxaparin sodium	Lovenox®	2
2016/2017	Etanercept	Enbrel®	2
2017/2018	Adalimumab	Humira®	8
2017	Insulin lispro	Humalog®	1
2017	Rituximab	Rituxan®	6
2017	Teriparatide	Forteo®	2
2017/2018	Trastuzumab	Herceptin®	5
2018	Bevacizumab	Avastin®	1
2018	Pegfilgrastim	Neulasta®	5

TOTAL APPROVALS = 58*

*4 (2 filgrastim, 2 somatropin) were withdrawn in 2011, 2012, 2016, 2017

European Medicines Agency. www.ema.europa.eu (accessed Jan 14, 2019)
Generics and Biosimilars Initiative. http://gabionline.net/Biosimilars/General/Biosimilars-approved-in-Europe. (accessed Jan 14, 2019)

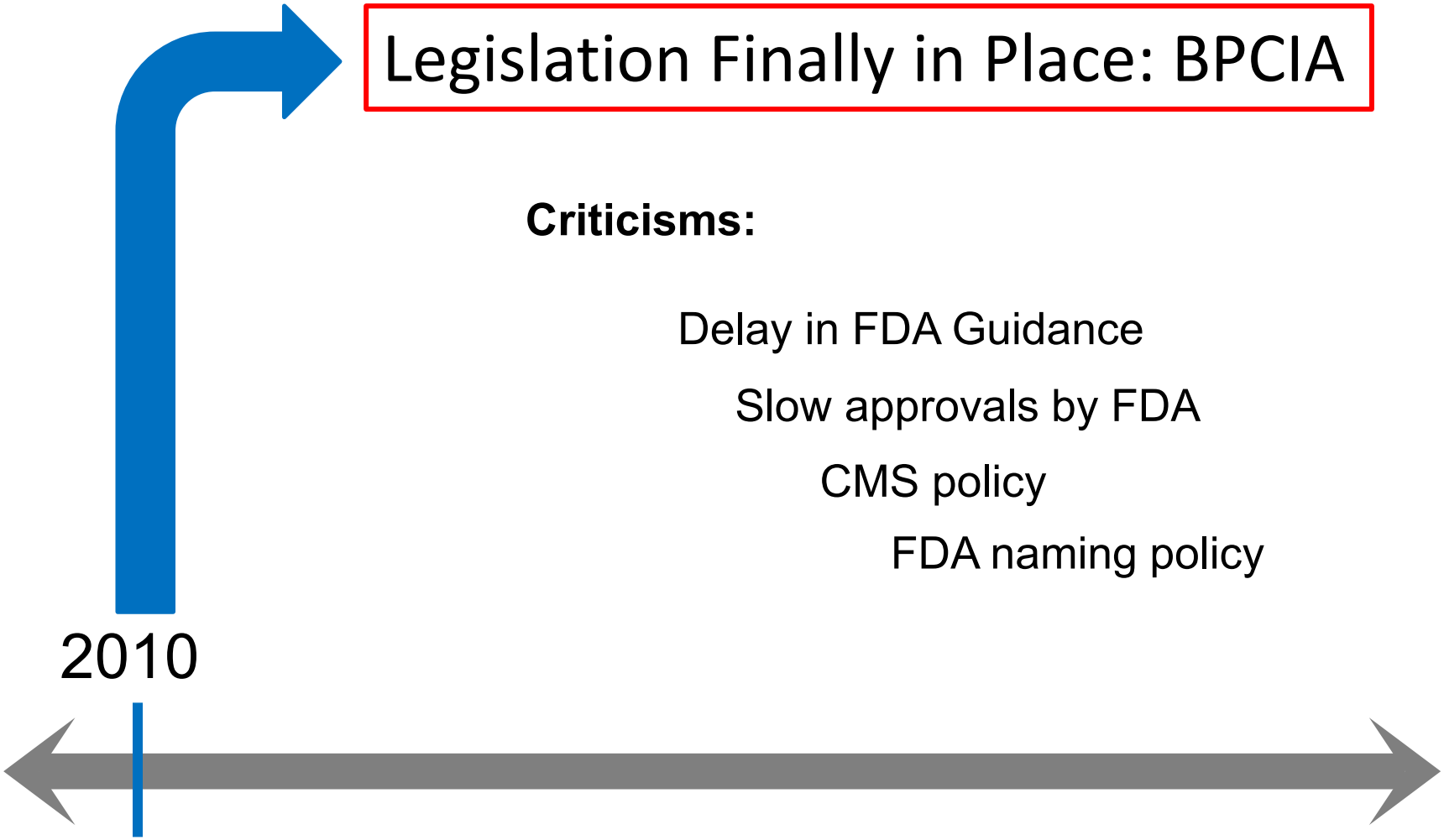
Biosimilar Sales



Adapted from: International Generic and Biosimilar medicines Association (IGBA). 2018. "Building on the Experience and Success of Biosimilar Medicines." February 1. www.igbamedicines.org/doc/Module6.pdf

Barriers to Biosimilar Utilization

Factors Influencing U.S. Biosimilar Utilization



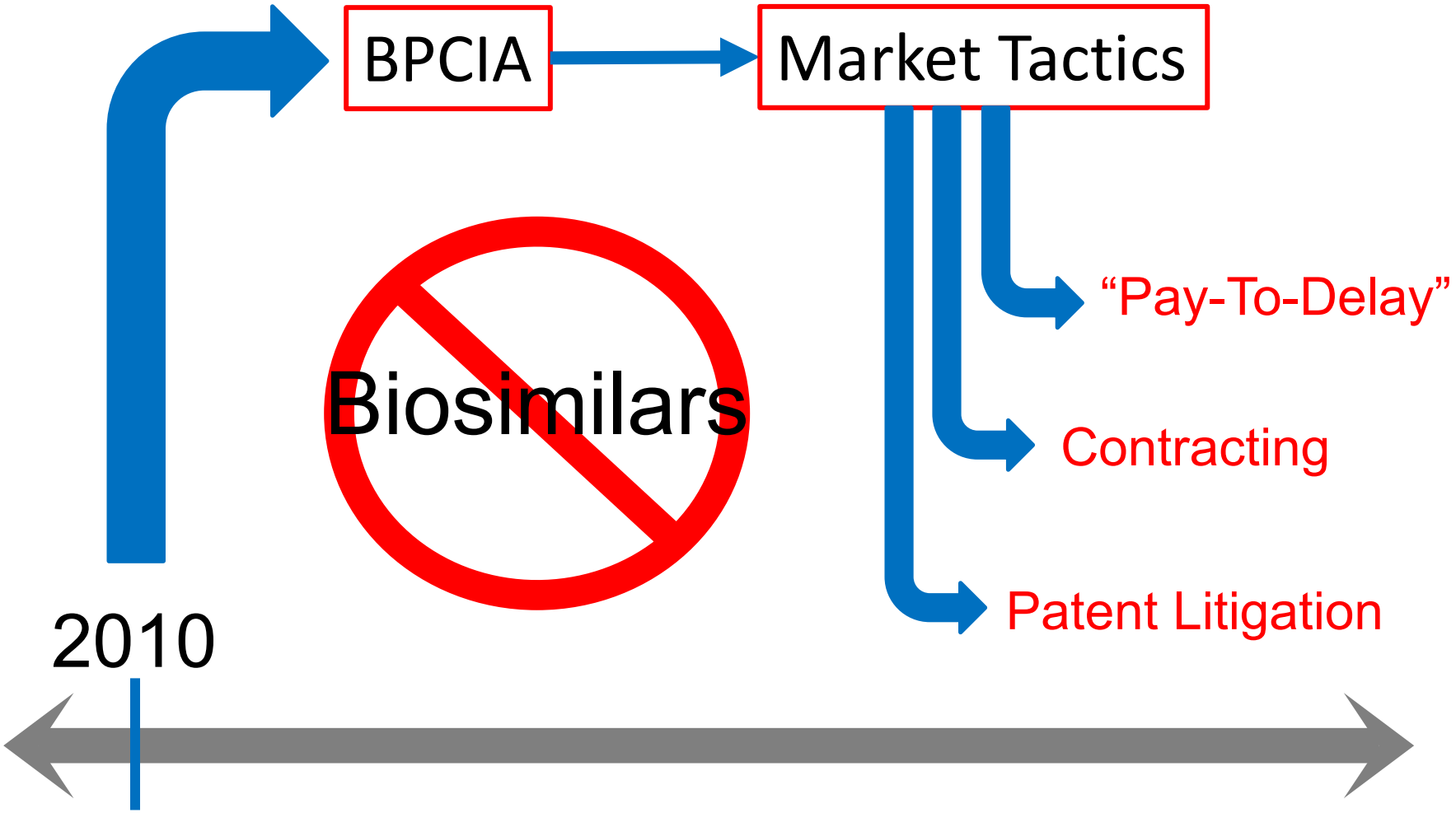
www.fda.gov
Brill A, Robinson C. Steps to reducing barriers to biosimilars in the U.S. 2018. www.getmga.com.

FDA Biosimilars Action Plan (BAP)

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.

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/UCM613761.pdf

Factors Influencing U.S. Biosimilar Utilization



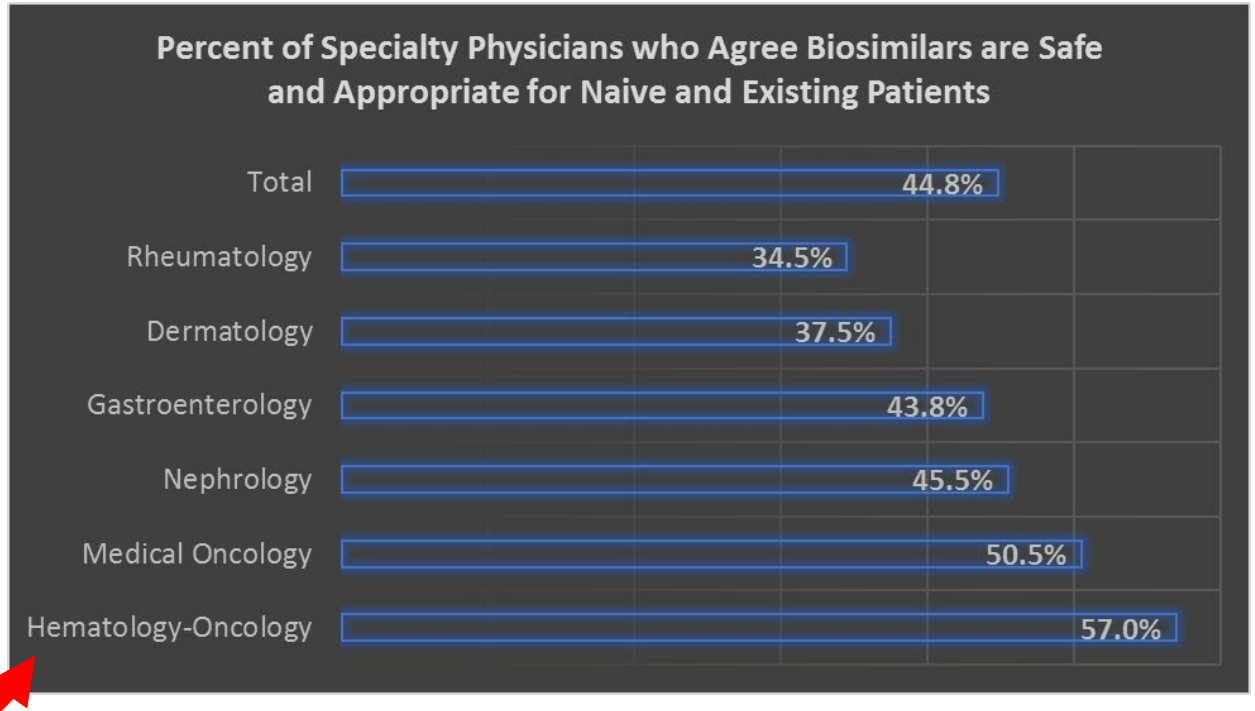
Brill A, Robinson C. Steps to reducing barriers to biosimilars in the U.S. 2018. www.getmga.com.

Factors Influencing U.S. Biosimilar Utilization

Uncertainty - Prescribers

Adapted from: Cohen et al. **Awareness, Knowledge, and Perceptions of Biosimilars Among Specialty Physicians**. *Adv Ther* 2017;12(2):2160-2172.

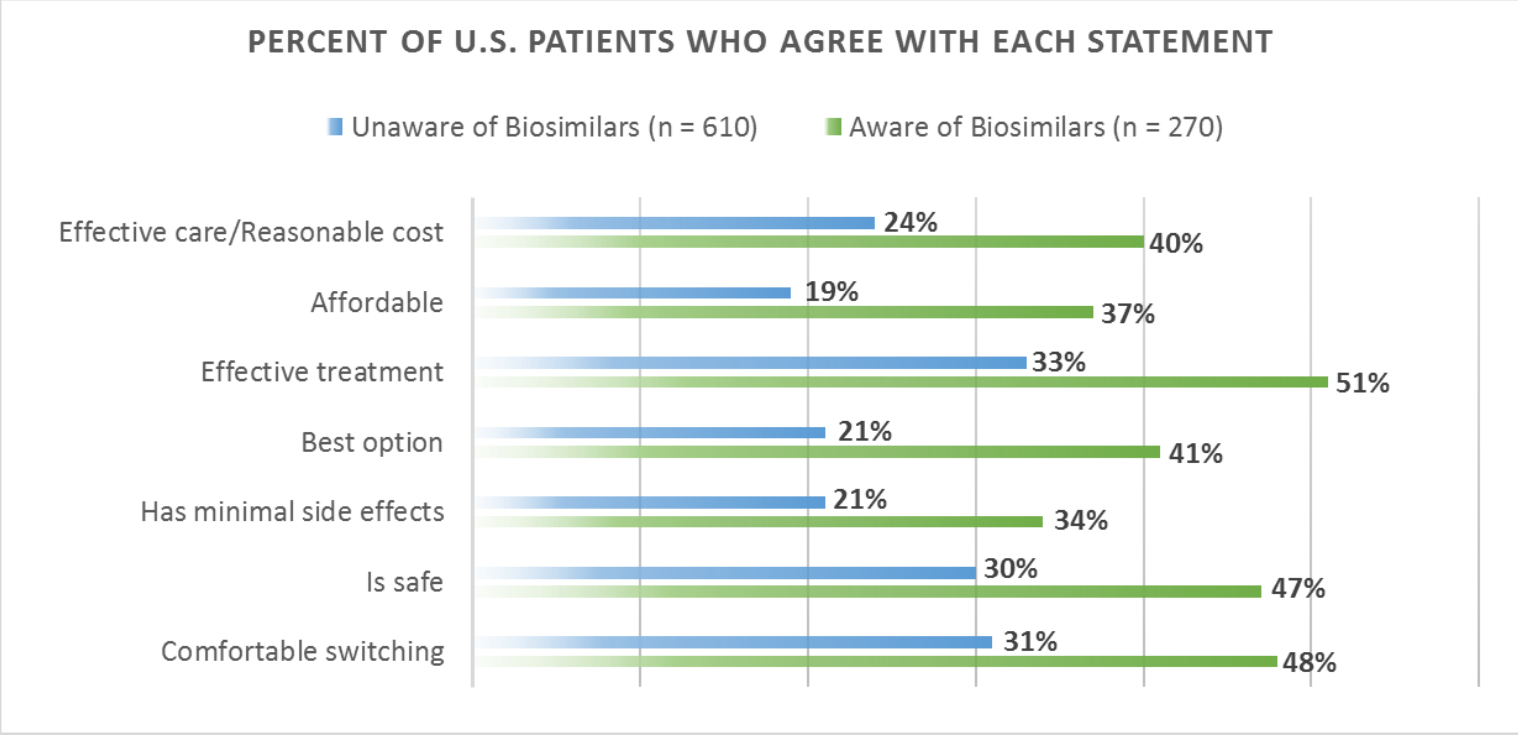
- **1,201 US physicians** in specialties that are high biologics prescribers
- **75%** trust the FDA approval decisions, but…
- When asked if they believe biosimilars are safe and appropriate for naïve and existing patients….



Factors Influencing U.S. Biosimilar Utilization

Uncertainty - Patients

Adapted from: Jacobs et al. **Patient attitudes and understanding about biosimilars: an international cross-sectional survey**. *Patient Preference and Adherence* 2016;10:937-948.



- 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

Medical Specialists' Attitudes to Prescribing Biosimilars
Pharmacoepidemiol Drug Saf 2017;26(5):570-577.

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

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

OPPORTUNITY FOR EDUCATION

Biosimilars:
Data Sources for Decision-Makers

Data Source – Clinical Trials

Strengths:

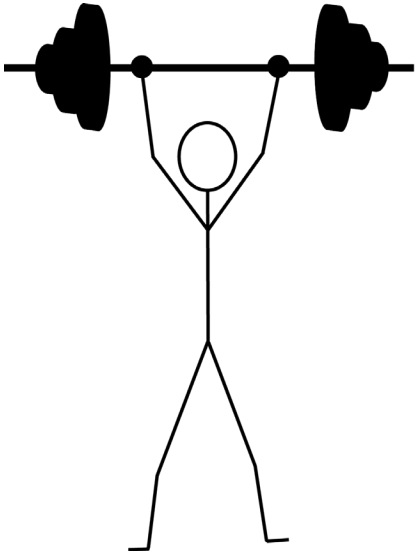
Randomized Controlled Trials (RCTs) = **GOLD STANDARD**

Carefully designed to **reduce**:

BIAS

CONFOUNDING

PLACEBO EFFECT

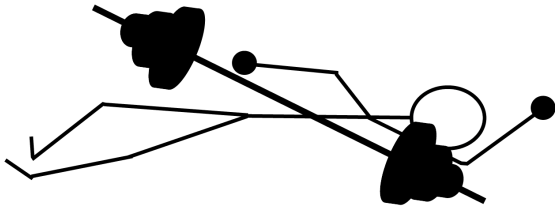


Hannan EL. *J Am Cardiol Intv*. 2008;1(3):211-217.

Data Source – Clinical Trials

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



Greenfield. *Value in Health* 2017;20:1023-4.
Jarow, et al. *JAMA* 2017;318(8):703.

Origins in the Gap in Evidence

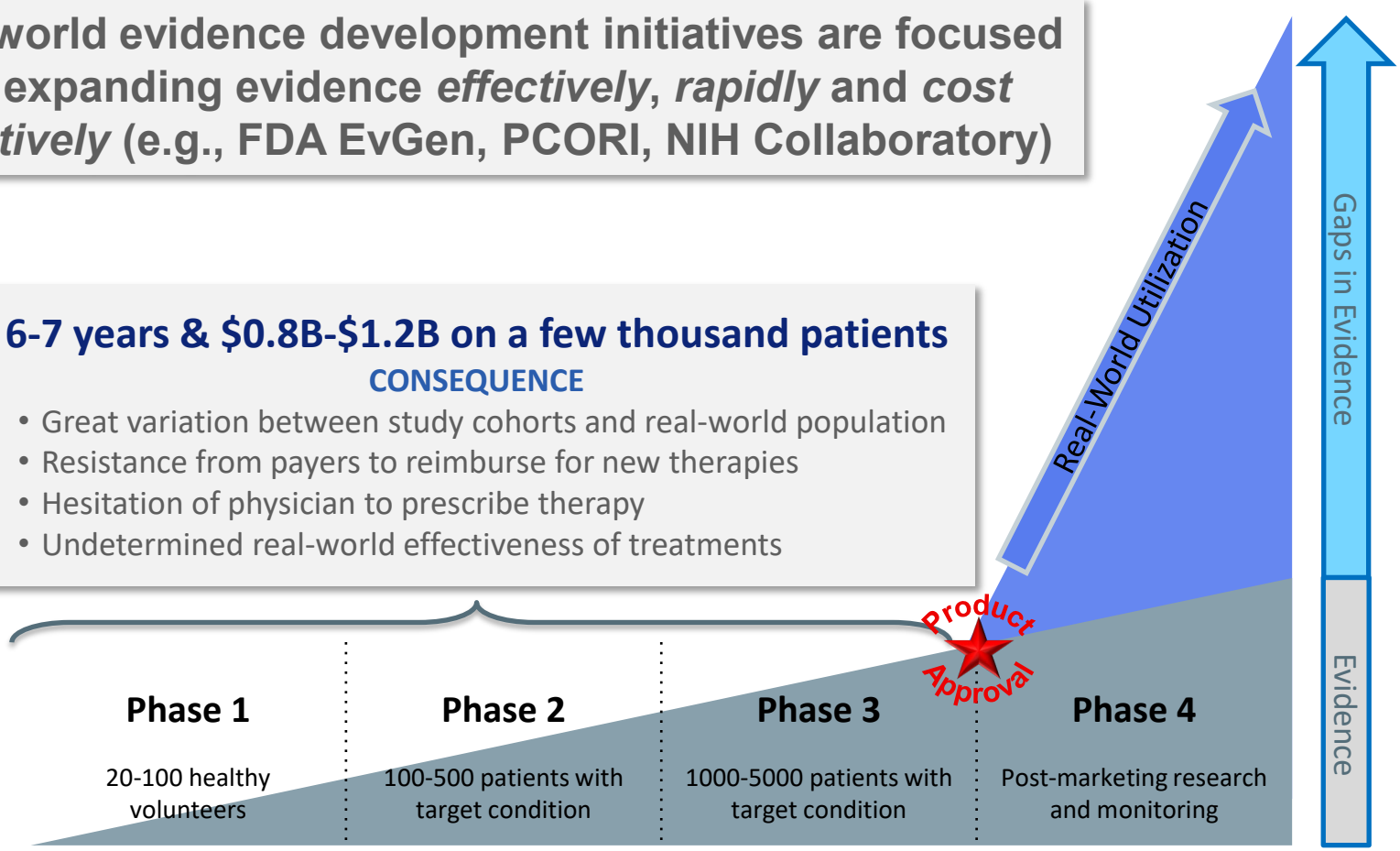
Real-world utilization quickly outpaces available clinical evidence

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

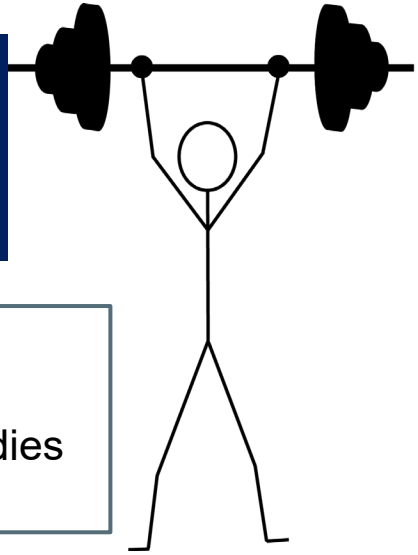


Data Sources – Real World Evidence

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



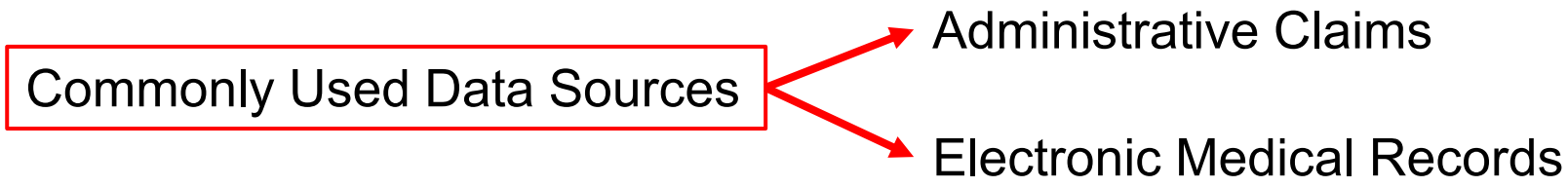
"…on average, there is little evidence for significant effect estimate differences between observational studies and RCTs, regardless of specific observational study design, heterogeneity, or inclusion of studies of pharmacological interventions." – Anglemyer et al.

https://healthpolicy.duke.edu/sites/default/files/atoms/files/rwe_white_paper_2017.09.06.pdf
Greenfield. *Value in Health* 2017;20:1023-4
Jarow et al. *JAMA* 2017;318(8):703.
Anglemyer et al. Cochrane Database Syst Rev 2014 Apr 29;(4):MR000034

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?

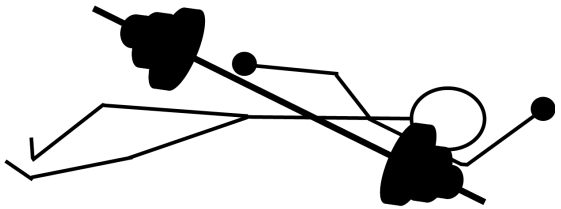
- Payment/billing
- Document clinical care
- Physician decision support
- Recordkeeping
- Registries
- Data provide rich source of information for patient safety evaluations

Platt R, et al. The U.S. Food and Drug Administration's Mini-Sentinel program: status and direction. Pharmacoepidemiol Drug Saf. 2012 Jan;21 Suppl 1:1-8.

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



Hannan EL. *J Am Cardiol Intv*. 2008;1(3):211-217.

Patient-Generated Data

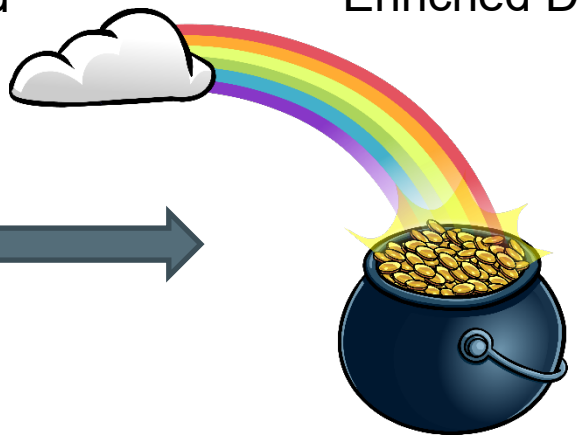
- Not just a PRO Instrument anymore…
  - Wearable devices
  - Mobile phone applications
  - Social Media

- Mobile app
  Social Media

- Electronic Health Record
- Administrative Claims

- Enriched Data

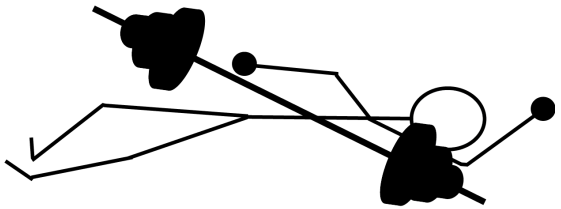
LINK



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



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BBCIC:
One Approach to
Real-World Evidence Generation

BBCIC - Background

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

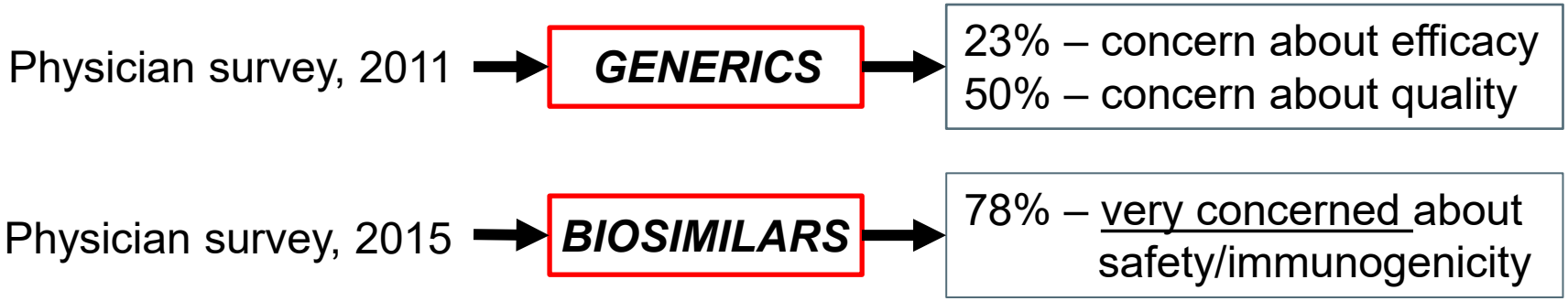
BBCIC Purpose: Why the BBCIC Is Needed

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.



- Shrank et al. Ann Pharmacotherapy, 2011;45(1):31-8.
- http://www.gastro.org/press_releases/2015/7/29/national-survey-reveals-gastroenterologists-views-on-biosimilar-drugs

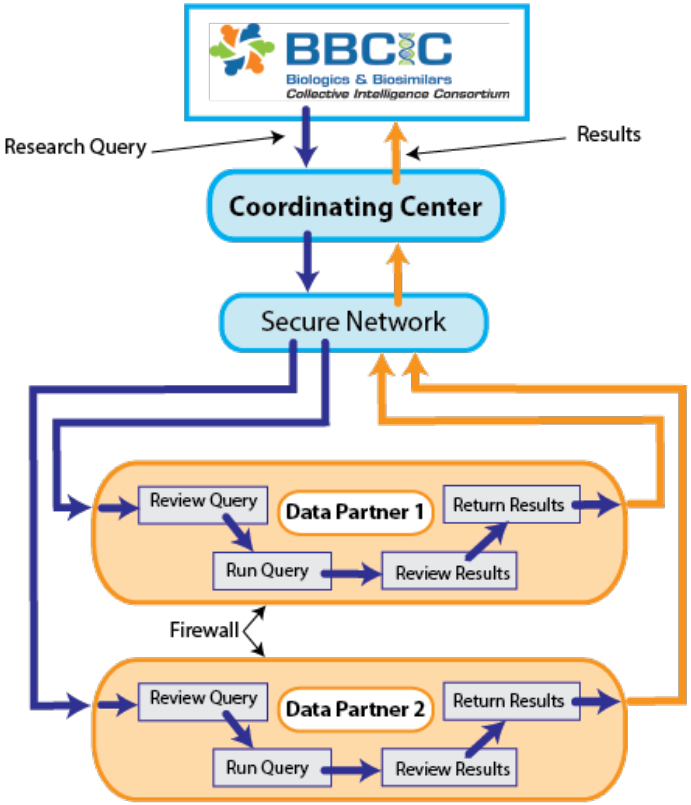
BBCIC Surveillance – Leveraging Sentinel Capabilities

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

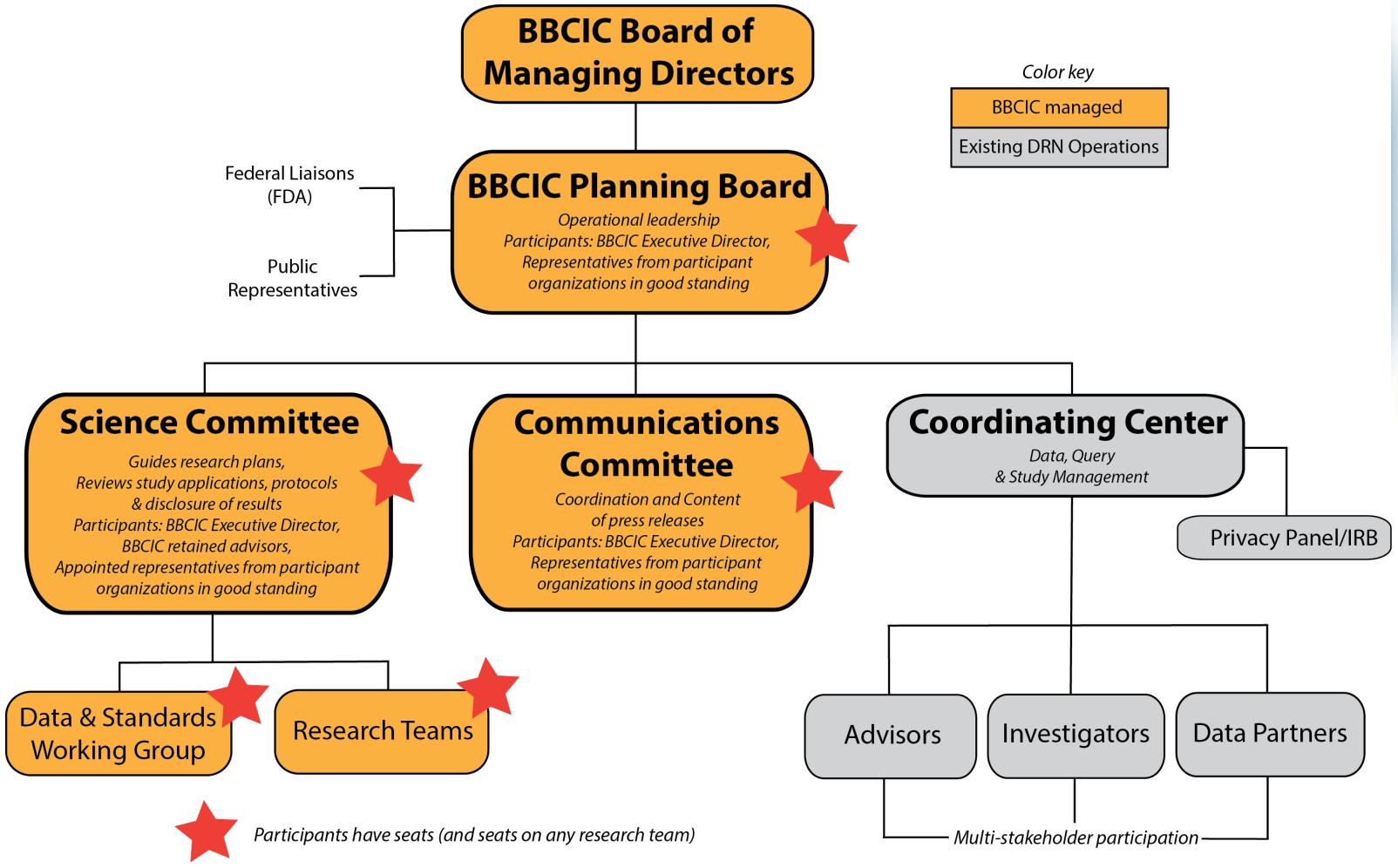


A forum for collaboration between managed care organizations, integrated delivery networks, PBMs, pharma companies and research institutions

BBCIC Governance Overview

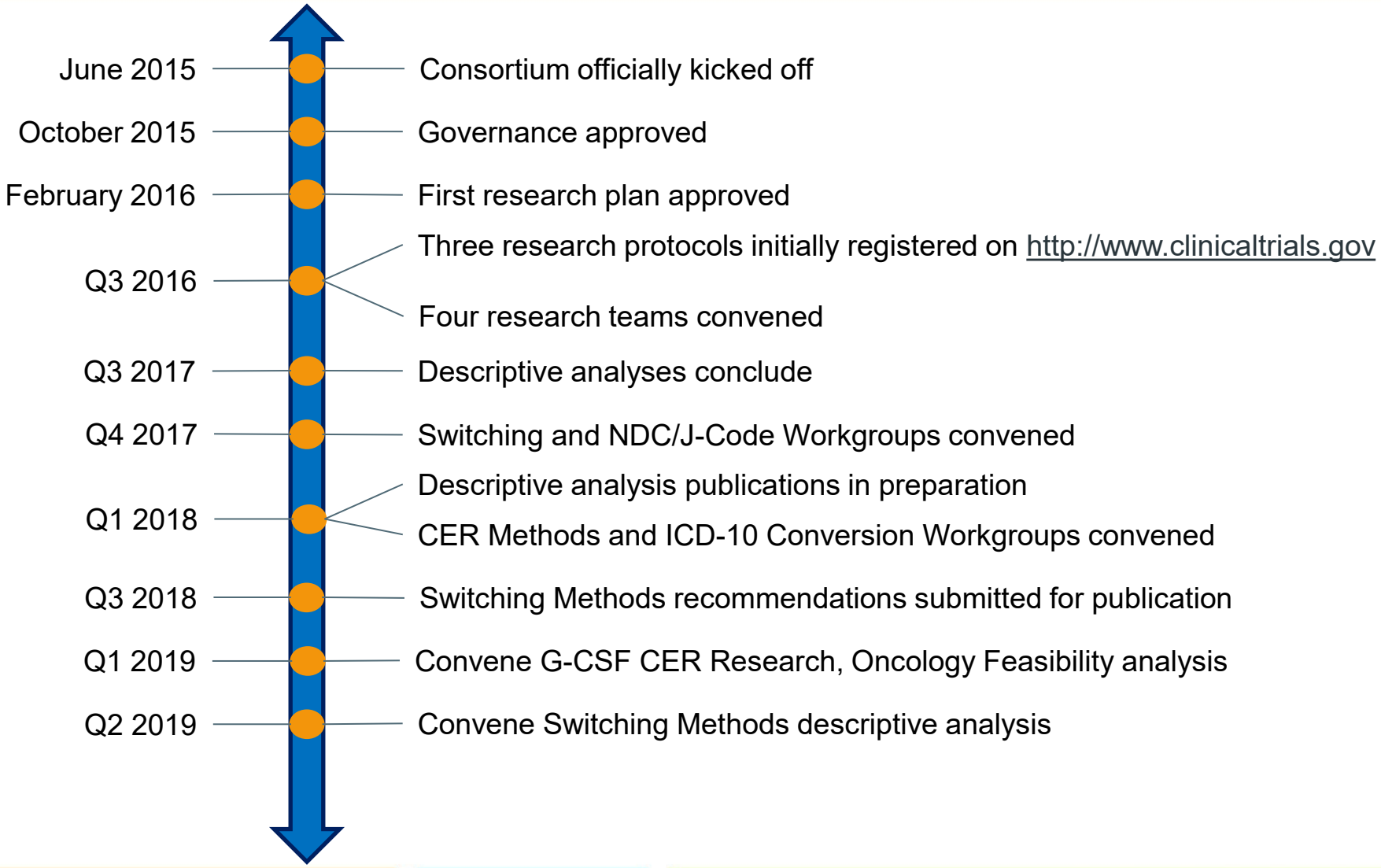
- The BBCIC Charter outlines transparent organized process for conducting research. There are no surprises.
- CER protocols, designed by KOLs and following ISPOR-ISPE guidelines, must explicitly pre-specify the epidemiologic, statistical and clinical thresholds required to identify a safety-related finding.
- 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 Governance Overview



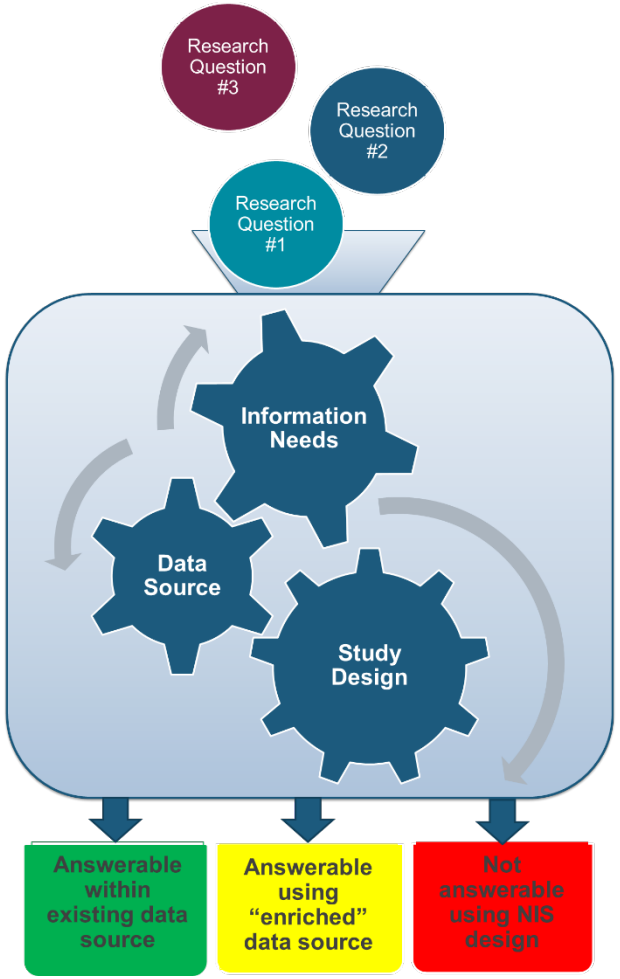
AbbVie
Aetna
Amgen
Anthem
Boehringer
Express Scripts
KP Washington
Harvard Pilgrim
HealthPartners
HOPA
Henry Ford
Optum
Sandoz

BBCIC Progress to Date



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

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

Descriptive Analysis Research Teams

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

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

- 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**

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

BBCIC - Progress

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

Workgroups

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

Project	Challenges Addressed	Study Goal
Switching	• Design Considerations	Treatment of switching/sequencing as a covariate/confounder in BBCIC CER studies
CER Methods	• Design Considerations	Develop best-practices based on current methodology for conducting observational comparative-effectiveness research
NDC / J-Code	• Exposures • Outcomes	Investigate the extent to which NDCs are being supplied on physician-office claims
ICD-10 Mapping	• Exposures • Outcomes	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.

2018 Presentations

5 Podium Presentations

- ICPE
- ISPOR
- DIA
- AMCP Nexus
- NW AMCP

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7 Poster Presentations

- HCSRN
- ICPE
- AMCP Nexus

BBCIC - Progress

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

2019 Planned Publications

Insulins	• **In Progress**: A pair of companion manuscript completing internal review • **Next Steps:** January submission planned to the *Journal of Managed Care & Specialty Pharmacy*
G-CSF	• **In Progress**: Manuscript in preparation
Anti-Inflammatories	• **In Progress**: Internal review underway • **Next Steps:** February submission planned to the *Journal of Managed Care & Specialty Pharmacy*
ESA	• **In Progress**: Final report in preparation • **Next Steps:** Report will be posted on www.BBCIC.org
Switching	• **In Progress**: Manuscript under review at *Pharmacoepidemiology & Drug Safety* • **Next Steps:** Respond to peer-review revisions, resubmit
CER Methods - review	• **Completed:** Literature review and report have been prepared • **Next Steps:** Prepare a manuscript
CER Methods – best practices	• **In Progress:** Final Report prepared based on Workgroup meetings, undergoing internal review • **Next Steps:** Abstracts; Manuscript
"Gaps" Paper	• Opportunity to describe the state of observational research, challenges and gaps we have identified, and our efforts to address the gaps and opportunities • **In Progress:** Draft outline • **Next Steps:** Prepare manuscript; May submission planned

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 Q1 2019.

Insulins

The topic of a PCORI grant application.

DESCRIPTIVE ANALYSIS

Oncology Data Feasibility and 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.

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:

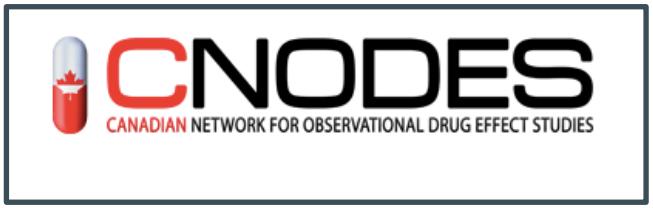
ENGAGEMENT

- Health Plans
- Patients
- Pharmacy Benefit Managers
- Manufacturers
- Prescribers and Healthcare Practitioners

Sources of Post-Marketing Data

Rapidly Evolving Landscape

https://fda.gov



https://www.cnodes.ca

https://pcornet.org

Sources of Post-Marketing Data for BIOSIMILAR Research

Post-Marketing Research - BIOSIMILARS

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

QUESTIONS?

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