October 29-November 1

Gaylord National Harbor • National Harbor, MD

AMCP

NEXUS2019

The Intersection of Value and Care

[R5] Biosimilars in the United States: Barriers, Solutions, Real-World Evidence, and the Experience of One Health System

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Learning Objectives

1. Describe the current approval and marketing status of biosimilars in the United States.
2. Recognize lingering barriers to uptake and utilization of biosimilars.
3. Explain the role of real-world evidence in supporting biosimilar utilization.
4. Discuss the experience of one hospital where biosimilars are being used.

Instructional Slide

- AMCP will add Housekeeping slides related to learning objectives, full faculty information, financial disclosures, ACPE info, audience polling instructions, etc
- Moderator will be covering these housekeeping slides

PRE-TEST

LQ1: Of the 23 biosimilars that have been approved in the U.S. to date, how many are available on the market?

a) 4
b) 9
c) 17
d) 23

LQ2: Among U.S. prescribers in specialties where biologics are frequently prescribed, what is the percent who trust biosimilars are safe?

a) Between 10% and 20%
b) Between 40% and 50%
c) Between 60% and 70%
d) Between 80% and 90%

LQ3: All of the following are limitations of commonly-used real-world data sources, EXCEPT:

a) Data are typically collected for reasons other than research
b) Market uptake may influence research capabilities
c) Clinical effectiveness outcomes may be challenging to identify
d) Data are usually randomized

LQ4: Which is a barrier to biosimilar adoption within a hospital system?

a) Ongoing litigation prevents access to biosimilars
b) Uncertainty around reimbursement
c) Design of novel delivery technology
d) Both a and b
e) All of the above

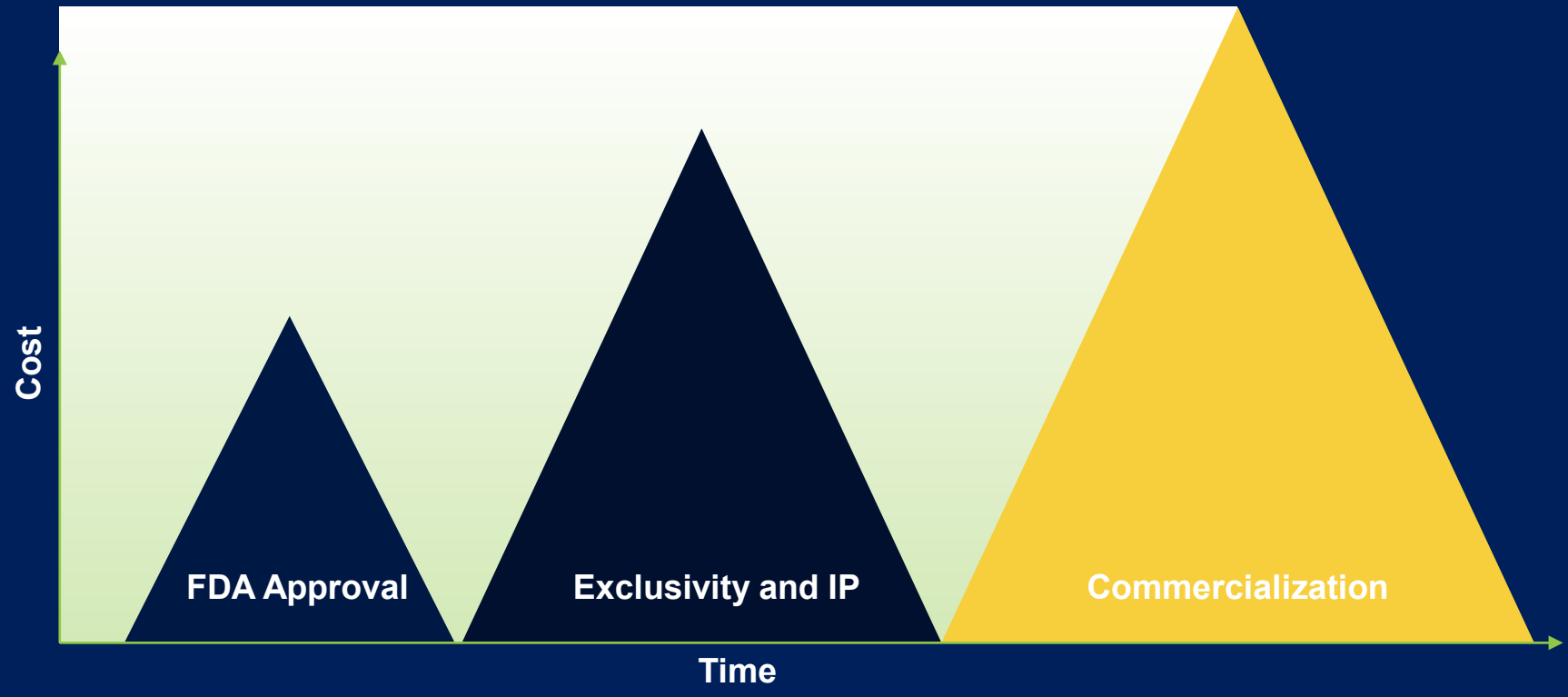
Agenda

- Biosimilars in the United States: current status
- Barriers to Biosimilar Utilization
- Real-World Evidence
- Yale New Haven Health System: Biosimilars in Practice

The Mountainous Challenges for Biosimilars in the US

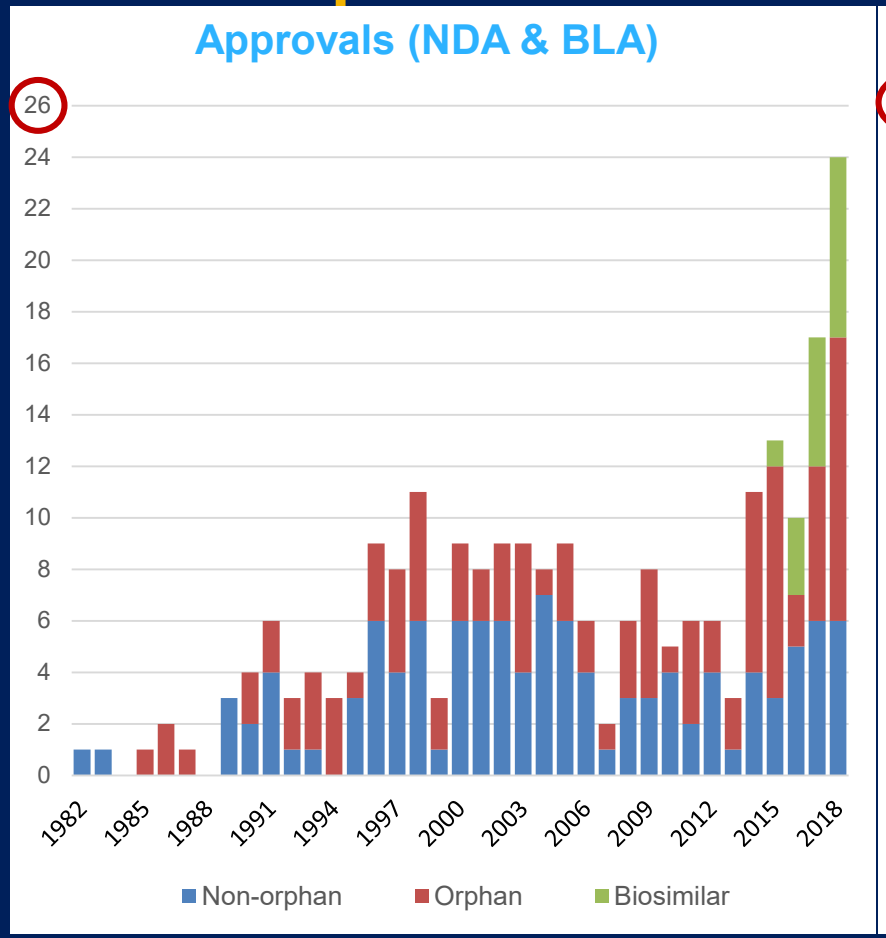
FDA approval is the first of a series of challenges

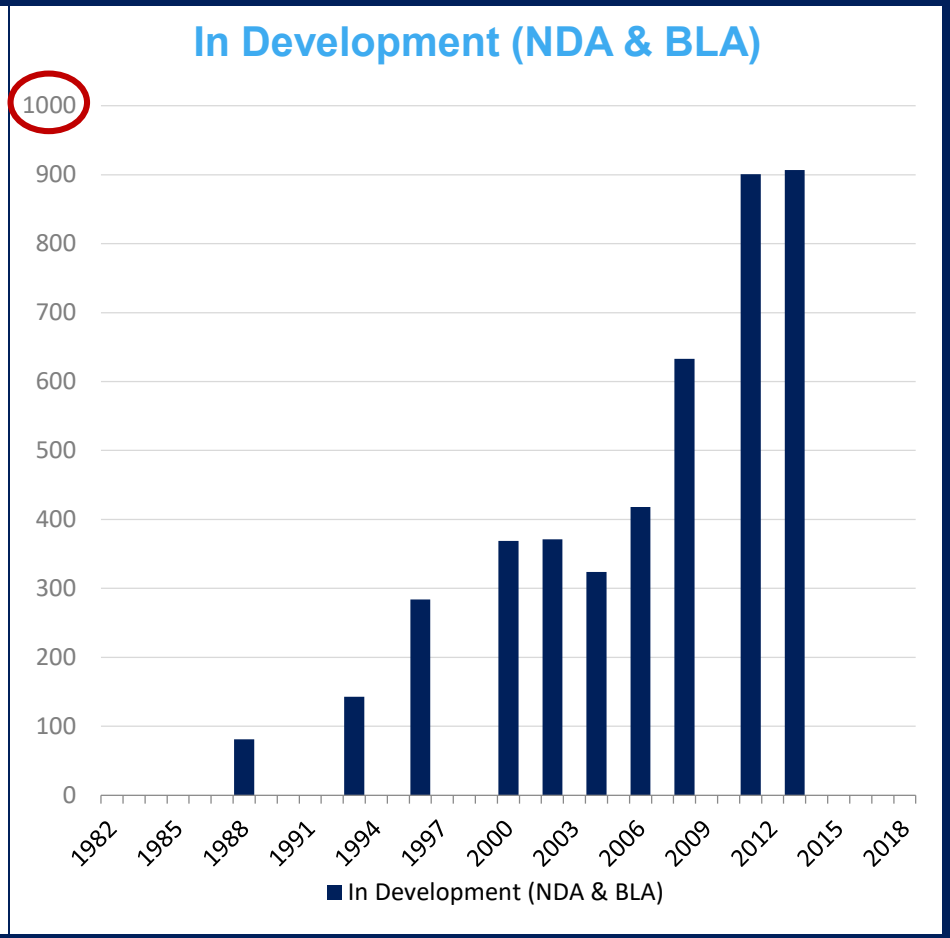
USA 23 approvals 9+ (unclear) 9 launches



Can there be a sustainable multisource specialty market in the US?

Biotech Approvals Have Increased and are Expected to Rise



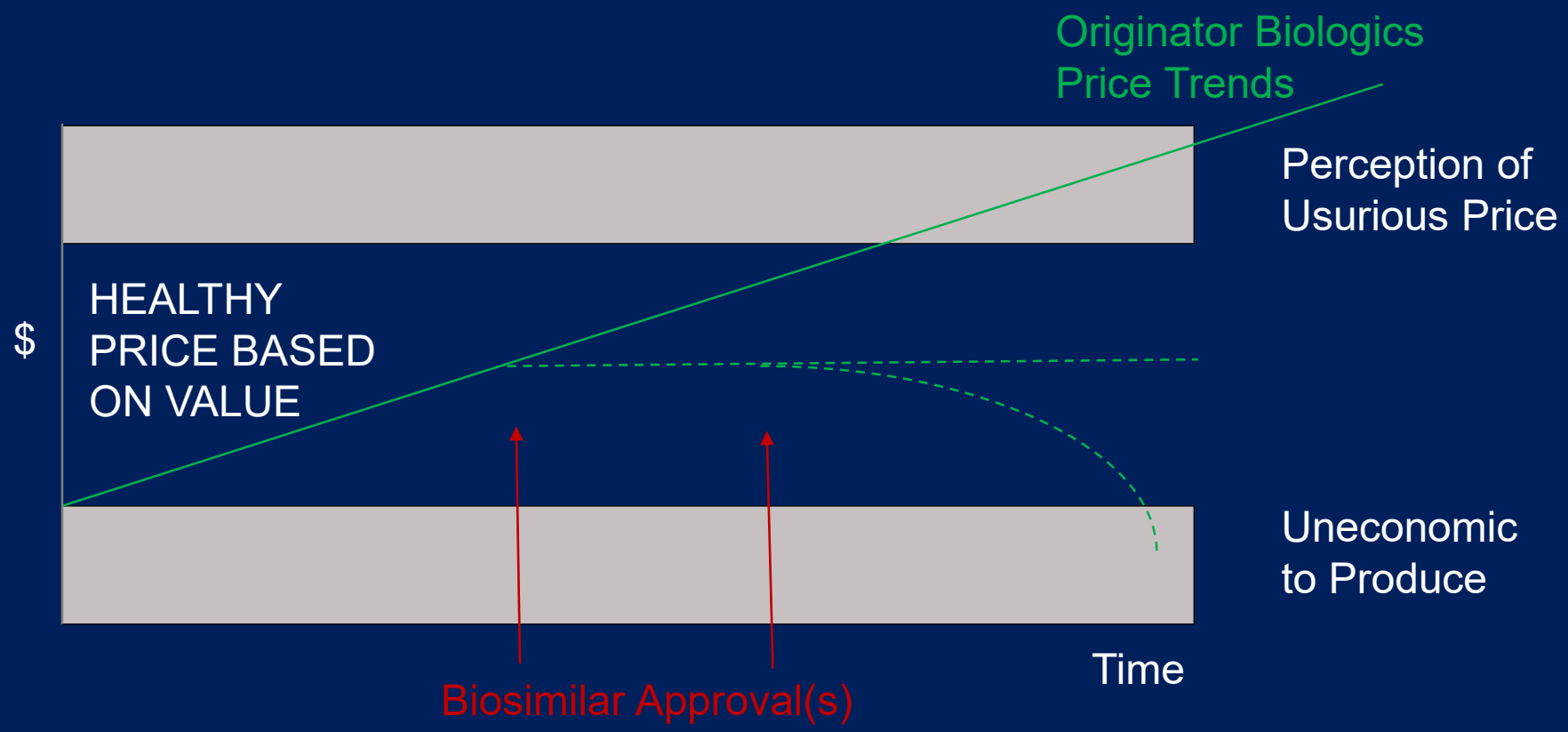


The science is the best it has even been; biotech is offering wholly new approaches to unmet medical needs. Competition based on value is key

1. FDA. "Drug and Biologic Approval Reports." Not including vaccines and blood products
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/default.htm
2. PhRMA. "Biotechnology Research Promises to Bolster the Future of Medicine with More Than 900 Medicines and Vaccines in Development." 2013. http://www.phrma.org/sites/default/files/pdf/biologics2013.pdf

Context: Public Recognition of Value of Biopharmaceuticals

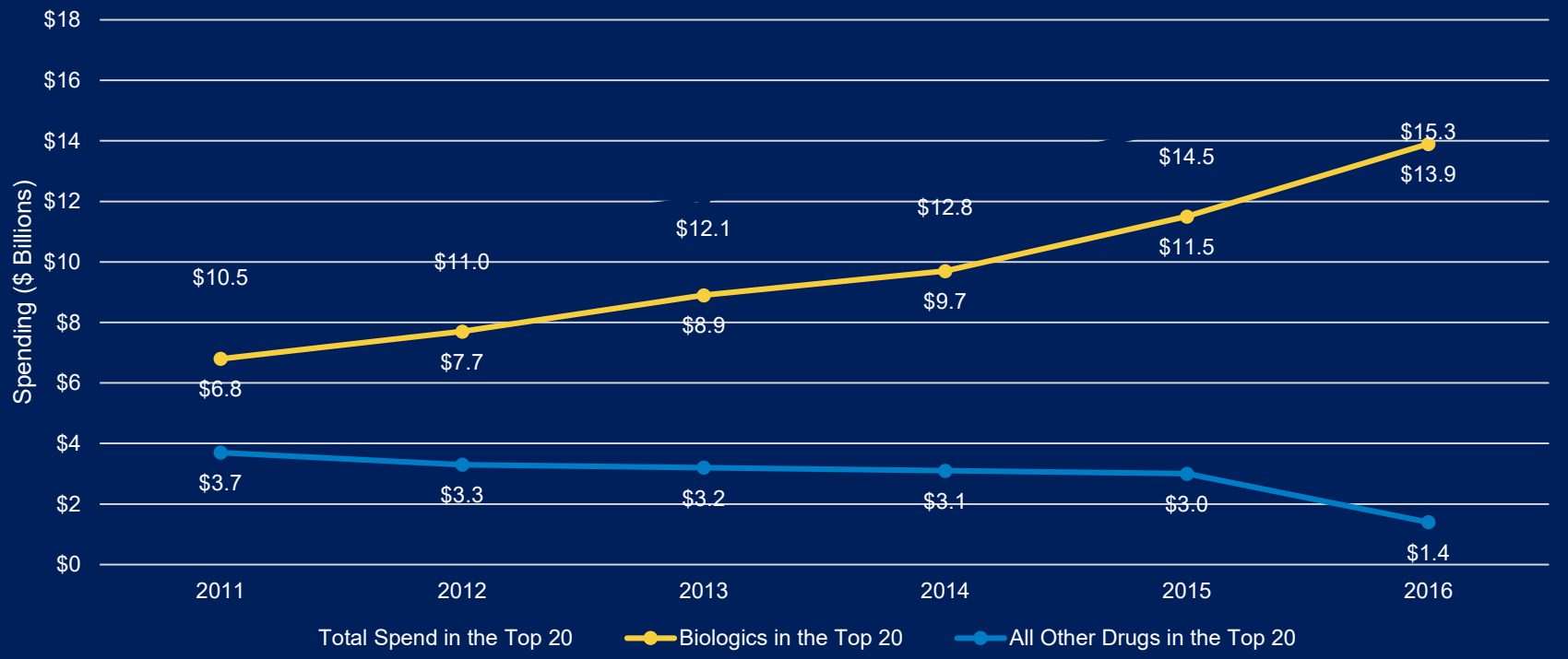
- VALUE IS A COMBINATION OF CLINICAL OUTCOME AND PRICE



To moderate prices mechanisms are needed to support competition amongst biologics irrespective of the regulatory pathway by which they are approved

US Biologics Market – Large and Increasing

- In 2016, biologics made up 91% of spending on the top 20 Part B



Obstacles to creating a multi-source biologics environment include complexity of development, prescribing patterns, interchangeability, physician reimbursement models, and payer coverage

Avalere Analysis of Medicare Part B and D Drug Spending Data. Available on CMS website: https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/MedicarePartB.html.

Avalere: Five Obstacles to Competition, 31May17 http://avalere.com/expertise/life-sciences/insights/five-obstacles-to-competition-in-the-united-states-biologics-market

What has happened recently at FDA more broadly…

- Statements and tweets from Dr. Gottlieb every day

  Dr. Gottlieb was only the Commissioner. He had to persuade those with power to implement change and make it stick. That was tested by his leaving

  What has actually happened:

  - Huge uptick in the number of FDA guidances issued[1], and other initiatives: Clinical trials transparency[2] including global initiatives[3]
  - Much higher visibility for the FDA, from flu vaccines[4] to cell therapy[5]
  - Addiction dominating headlines (nicotine and opioids)
  - USG Shut down, yet many initiatives sped up, e.g. complex generics, compounding
  - FDA, especially Dr. Gottlieb, had the confidence of the Administration, but very high pressure to deliver[6];
  - Dr. Gottlieb left; FDA Reorganization on 31Mar2019[7]

FDA with Dr. Gottlieb was no longer solely domestic nor just about approvals - he was forthright about economics and access; Ned Sharpless from NCI is less well known

1. Newly Added Guidance Documents here; 2. New steps FDA is taking to enhance transparency of clinical trial information to support innovation and scientific inquiry related to new drugs here; 3. product quality and transparency at foreign drug manufacturing facilities here; 4. Preparations for the upcoming flu season and vaccinations here; 5. policy steps and enforcement efforts to ensure proper oversight of stem cell therapies and regenerative medicine here; 6. Why Scott Gottlieb is the one Trump official everybody seems to like here; 7. FDA Reorg here

Biosimilars have had the Attention of the Trump Administration

A MASSIVE FLURRY OF ANNOUNCEMENTS BUT MUCH LESS CHANGE IN POLICY SUPPORT

- Trump Administration's "**American Patients First**" [1] July18 targets lower prices
- The FDA's **Biosimilar Action Plan (BAP)** issued Jul18[2] with a Public Meeting Sept18 and associated docket[3]. Broad and general goals
- **FDA 2019 Biosimilar Guidances**[4]
  - *Development of Therapeutic Protein Biosimilars: Comparative Analytical Assessment and Other Quality-Related Considerations; Draft Guidance for Industry, May 2019*
  - *Considerations in Demonstrating Interchangeability With a Reference Product; Guidance for Industry, May 2019*
- **Staff changes in the Biosimilar Product Development Team** at FDA under Congressionally endorsed FDA reorganization, but key appointments are Acting
- **Rollover** of those biologics regulated as drugs 23Mar2020, including Insulin – new guidance[5]

Biosimilars appear stuck in the regulatory weeds at FDA – no real focus on consistency in application of regulatory science to all biologics

1. HHS Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs16Jul18 here; 2. BAP 1Jul18 here; 3. Docket here; 4. FDA Biosimilar Guidance's here ;
5. FDA "Deemed to be a License" Provision of the BPCI Act here

Europe seems to be Succeeding... US not so much...

The impact of biosimilars in 2018: 'Treating a third more people, at half the cost'[1]

2018 saw an increase in the number of biosimilar approvals, and the expiry of patents on major products that allowed the entry of biosimilars across Europe.

07Jan19 By Ben Hargreaves

NBC NEWS

WORLD'S BEST-SELLING DRUG COSTS FIVE TIMES MORE IN US THAN EUROPE[2]

Critics accuse the maker of Humira of exploiting U.S. patent laws to keep competitors' less expensive versions off the market. The company, AbbVie, says it's balancing the need to keep the drug affordable to patients with the need to fund new drug development.

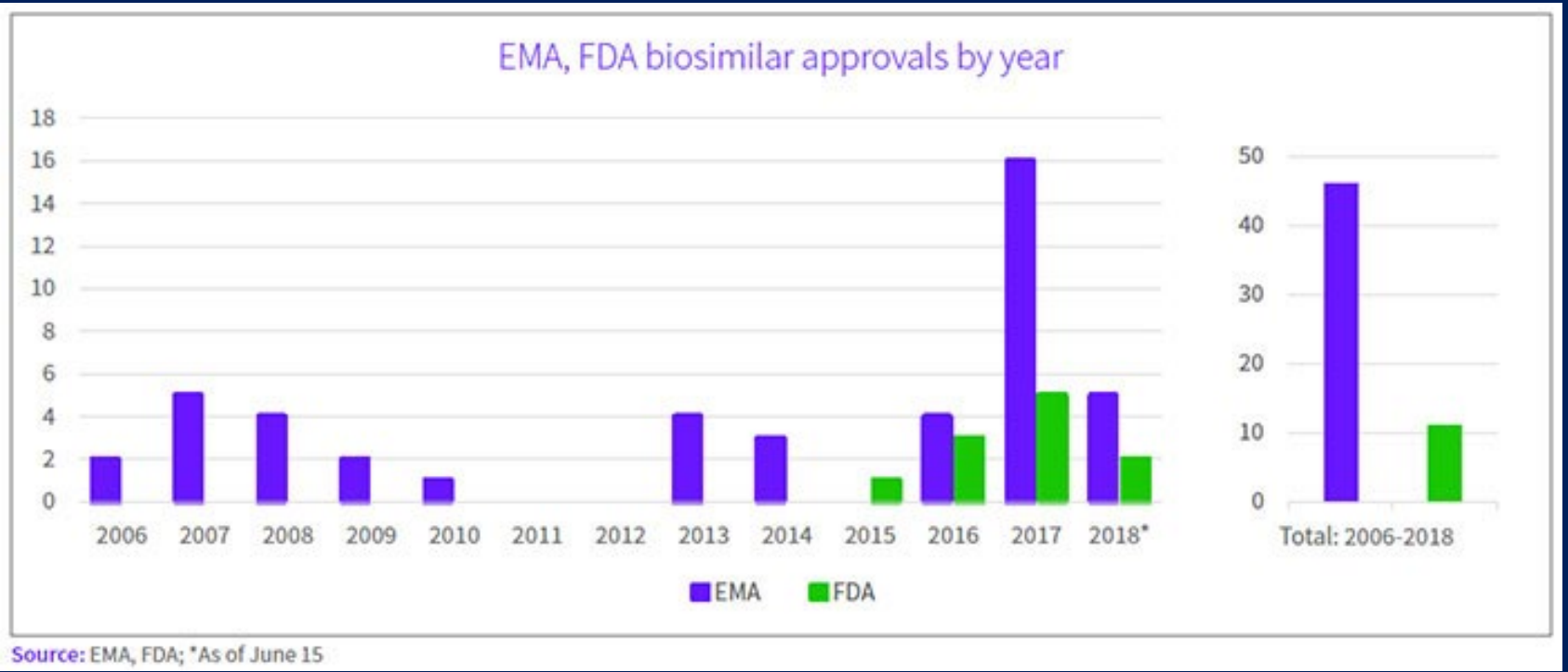
19Feb19

The US is the biggest market and yet struggling the most. This simply doesn't add up, or does it...

- https://www.biopharma-reporter.com/Article/2019/01/07/The-impact-of-biosimilars-in-2018
- https://www.nbcnews.com/nightly-news/video/world-s-best-selling-drug-costs-five-times-more-in-u-s-than-europe-1445064259924

Europe and the US still have different biosimilar approvals

YET US AND EUROPE ARE THE MOST HARMONIZED REGULATORILY

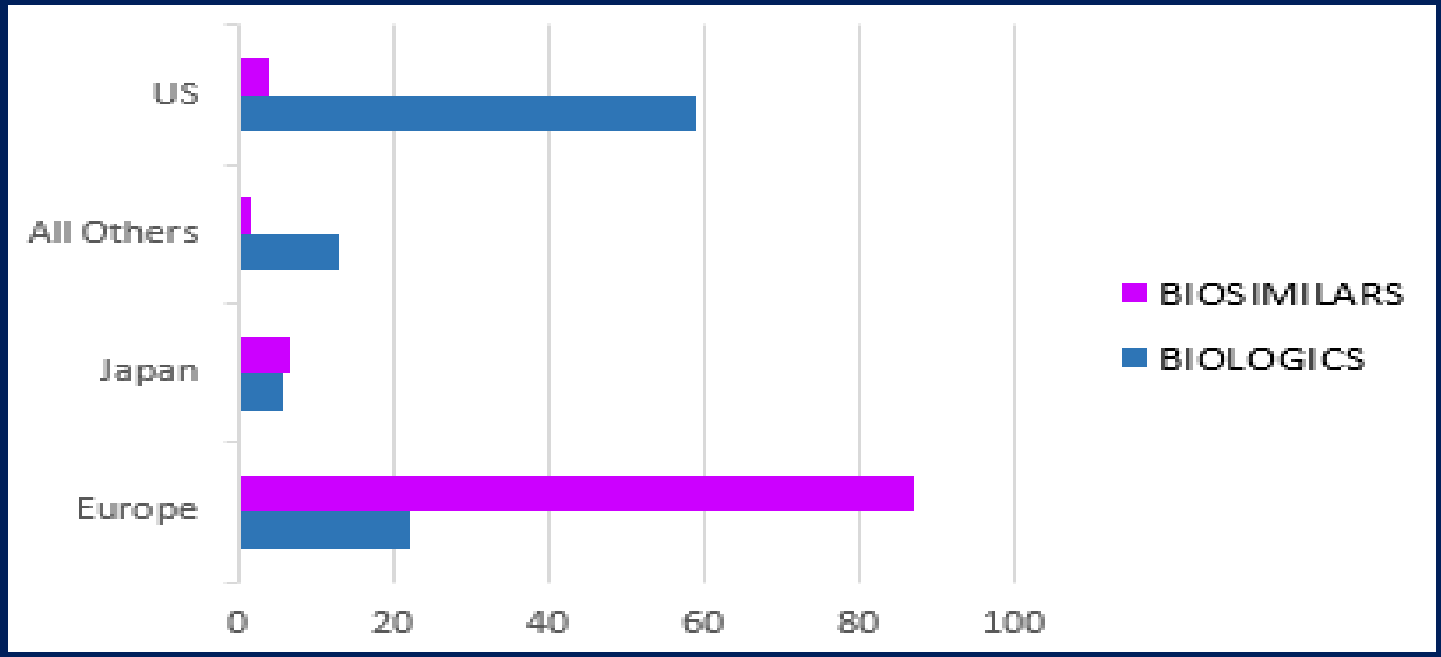


Requirements for different data in different regions are a problem and not scientifically justified – especially reference product

BioWorld *Will price competition follow in the wake of incoming U.S. biosimilar wave?* http://www.bioworld.com/content/will-price-competition-follow-wake-incoming-us-biosimilar-wave-0 (accessed 21Jun18)

Global Sales by % Total Market for Biologics & Biosimilars

- Worldwide Biosimilars STILL Face Considerable Challenges[1]



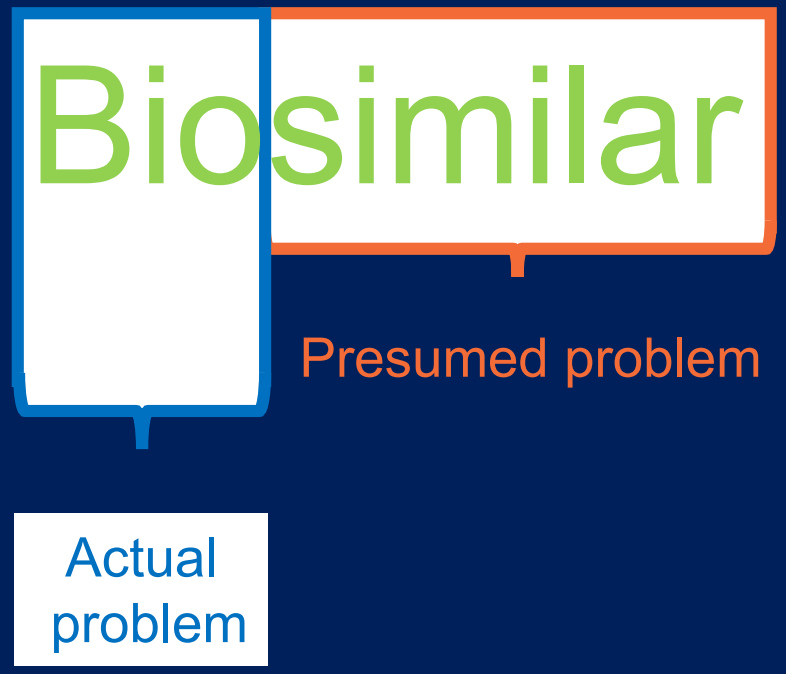
Biosimilar sales globally under 1 percent of those of originator biologics worldwide, so the room for further savings remain large and apply in, as well as well beyond, the US and Europe.

The global drivers for biologics competition are increasingly crucial for access worldwide. ... AND for access in the US

- http://biosimilarsforum.org/PDF/Biosimilars_WhitePaper-final.pdf
- IMS Health MIDAS MAT Q4 2016 - [$1,844,857,846 out of $246,643,913,154]

The Name Does Not Change The Product in the Tube

- Scientific and regulatory principles are established FOR ALL BIOLOGICS – ESPECIALLY IN THE US Consistent APPLICATION REMAINS A HUGE CHALLENGE



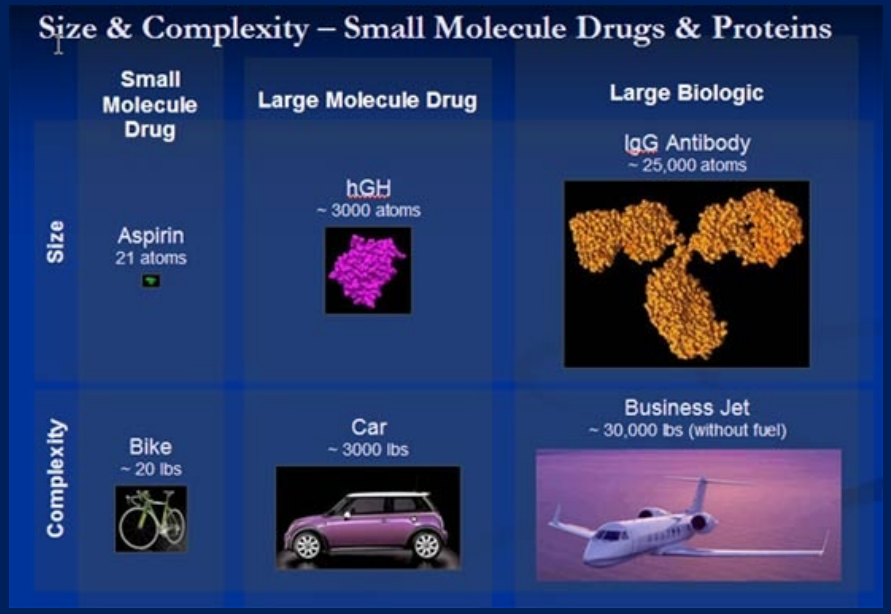
Without the message that the reference products vary too, biosimilars will continue to struggle to succeed in the US

Created through discussions with Ken Williams, Avalere

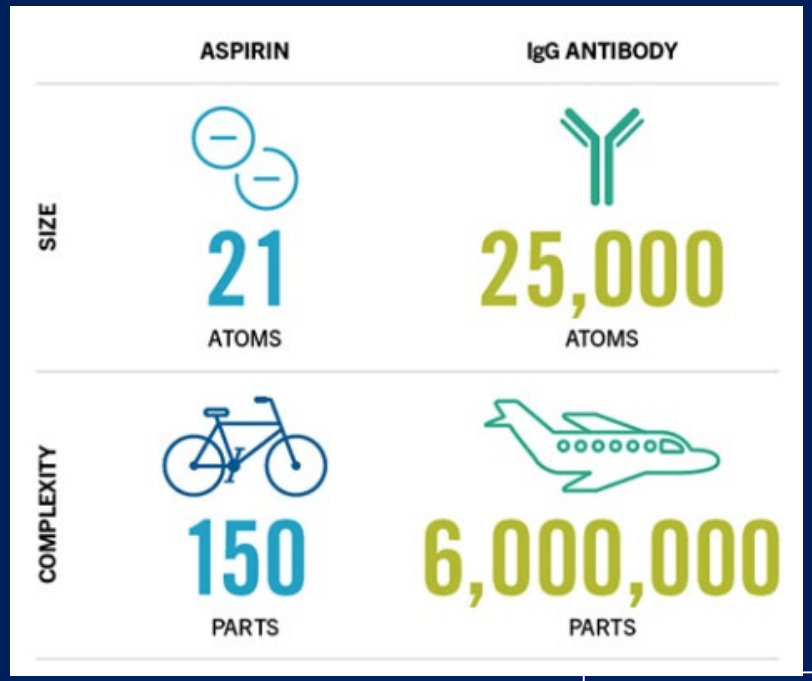
1. Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products April 1996 here

Standards Support Regulatory Decisions Worldwide

MANUFACTURING MUST BECOME *MORE EFFICIENT* IF MEDICINES ARE TO BE AFFORDABLE AND *THEREFORE* ACCESSIBLE



AZBIO



Genentech

But the wheels on those bicycles, cars and planes are equally round; complexity is not relevant.
NO NEED FOR EACH BIOLOGIC SPONSOR TO KEEP REINVENTING THE WHEEL

1. https://www.azbio.org/small-molecules-large-biologics-and-the-biosimilar-debate
2. https://www.gene.com/stories/similar-not-the-same-the-road-ahead-for-biosimilars?topic=oncology

The Reference is Global, the Biosimilars Needs to be too

- GOAL: Minimize repetitive studies that provide no new data – lack scientific & ethical validity

Biologic	Trade name	Sponsor	Countries in which 1st approvals were based on the same studies	Studies submitted for 1st approvals in > 1 country	Indications studied
Infliximab	Remicade	Janssen	US, EU, Canada, Australia	T16, T21	Crohn's disease
Etanercept	Enbrel	Amgen	US, EU, Canada, Australia	16.009, 16.014	Rheumatoid arthritis
Adalimumab	Humira	AbbVie	US, EU, Canada, Australia	DE009, DE011, DE019, DE031	Rheumatoid arthritis
Pegfilgrastim	Neulasta	Amgen	US, EU, Canada, Australia	980226, 990749	Febrile neutropenia in treatment of non-myeloid cancers
Bevacizumab	Avastin	Genentech/ Roche	US, EU, Canada, Australia	AVF2107g, AVF0780g	Metastatic colon cancer
Ranibizumab	Lucentis	Genentech	US, EU, Canada, Australia	FVF2598g, FVF2587g, FVF3192g	Age-related macular degeneration
*This is not necessarily a comprehensive list of the countries in which these studies were submitted for licensure of the product					

Same Registration Studies = Same Clinical Trials Material = Same Approved Product

Christopher J. Webster, Gillian R. Woollett (2017), "A 'Global Reference' Comparator for Biosimilar Development". BioDrugs doi:10.1007/s40259-017-0227-4
http://link.springer.com/article/10.1007%2Fs40259-017-0227-4

Interchangeability as a formal designation – Unique to US Law

Dr. Leah Christl, while at FDA, said[1] that **FDA agrees with the European regulators' conclusion that biosimilars are interchangeable with their reference[2] for the purpose of physician prescribing.**

However, she then explained in some detail that interchangeability in the US is a designation **solely for the purposes of substitution by other than the prescriber.** And for such pharmacist substitution the law was clear that an additional designation from FDA was available.

This FDA designation will confirm there being no basis for switching being a safety or efficacy concern[3]. Data showing a problem does not exist[4]

Semantics matter. Nonetheless regulatory consistency is essential to the future potential for harmonization

1. Medicines for Europe, 16th Biosimilars Mtg, London 26-27 April 2018; 2. Pekka Kurki et al, *Interchangeability of Biosimilars: A European Perspective* BioDrugs, DOI 10.1007/s40259-017-0210-0; 3. Managed Care Magazine, *FDA's Gottlieb Aims To End Biosimilars Groundhog Day*, 25Jan19, https://www.managedcaremag.com/archives/2019/1/fda-s-gottlieb-aims-end-biosimilars-groundhog-day; 4. Hillel P. Cohen et al *Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes* Drugs. https://link.springer.com/article/10.1007/s40265-018-0881-y

Harmonization and Regulatory Convergence Needed

- All clinical studies are a tax on patients and must add value
- Clinical studies that are unnecessary are ALWAYS unethical
- Meaningful data is way more than reassuring data, or nice to know – it is essential data

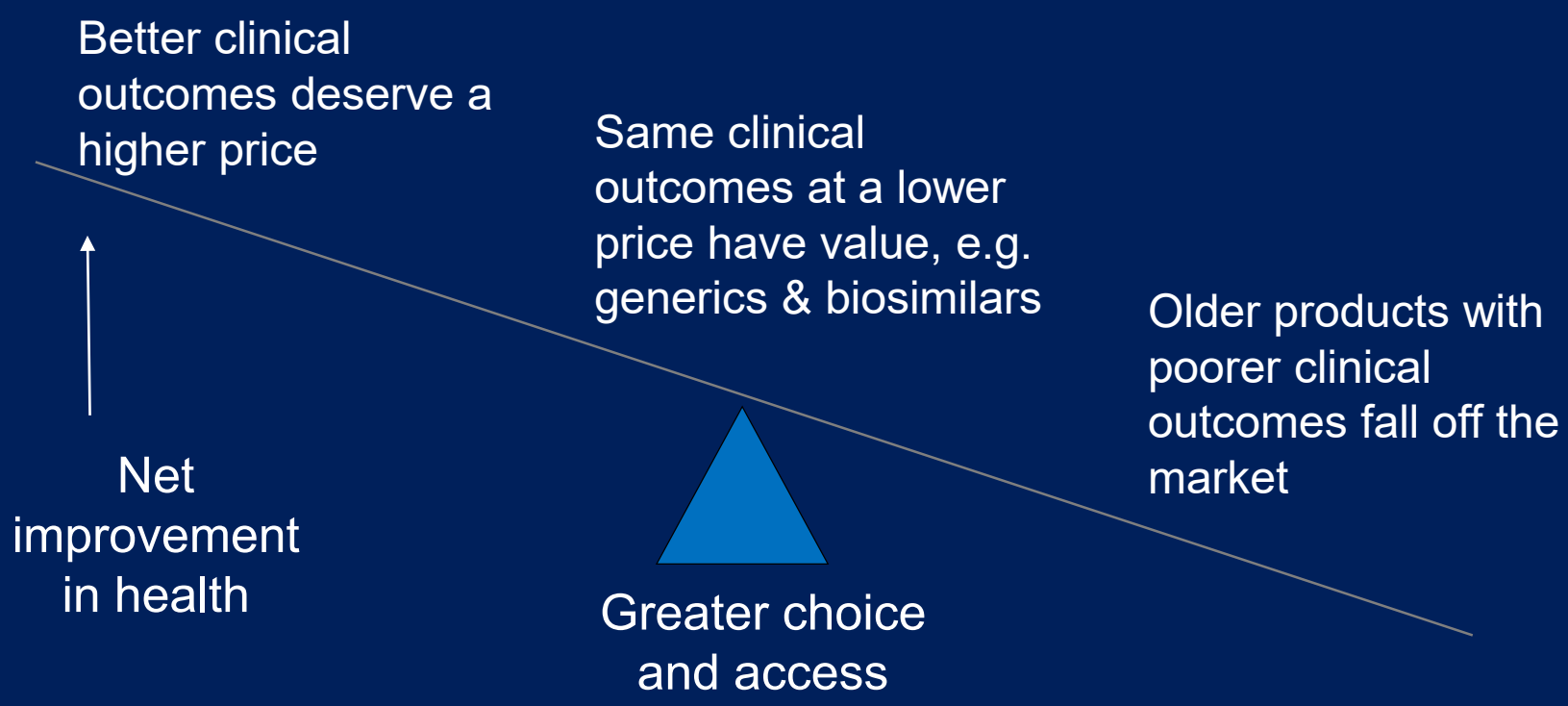
- Harmonization of pharmacovigilance allow better bigger data sets to be achieved more quickly and can supersede the requirements for PMS studies that are local. Initiatives are already underway, e.g. DQSA (US), 2-D barcodes (EU)
- Pre-agree data cutoffs after which PMS studies can be discontinued
- Real world evidence (RWE) and standards (USP)
- Optimize ROI across multiple jurisdictions to enable greater savings worldwide

Coordinated studies that provide data upon which actions can be taken in multiple jurisdictions concurrently creates predictability

Interchangeability of Biosimilars: A European Perspective here Jan 2017; *A 'Global Reference' Comparator for Biosimilar Development*. Here May 2017
An Efficient Development Paradigm for Biosimilars here Aug 2019; *Evolution of the EU Biosimilar Framework: Past and Future* here Sep 2019

Payer/ Provider Recognition of Value

- Value is a Combination of Clinical Outcome and price



That biosimilars offer the same clinical outcomes at a lower price is yet to be a recognized value, or even basic truth, in the US

Consumer Confidence in All Medicines Depends on Regulatory Consistency Based on Sound Science

- GLOBAL DEVELOPMENT OF ORIGINATOR BIOLOGICS IS AN ACCEPTED NORM
  - Both access and affordability of medicines depend on efficient development to accepted clinical standards and norms (e.g. Declaration of Helsinki, ICH[1], ICMRA[2])
  - High standards can seem unaffordable, but lesser standards unacceptable so what is needed is leveraging data cross-jurisdictionally to the right standard – it is the presumed norm for originator medicines and generics
  - The highly regulated markets traditionally get the earliest access, but there is increasing intolerance to delayed access for other jurisdictions
  - New mechanisms are being sought to facilitate access by minimizing unnecessary repetition of already unnecessary studies, especially clinicals (e.g. WHO Prequalification of Vaccines and Biosimilars), and regulatory hurdles (e.g. Inspections)

Trust in regulatory authorities and the basis of their decisions is critical. Yet FDA still adding more demands biosimilars already approved elsewhere... ...and yet more for an IC designation

1. International Committee for Harmonization http://www.ich.org/home.htm
2. International Pharmaceutical Regulators - *ICMRA statement about confidence in biosimilar products (for healthcare professionals* here*), (for patients and the public* here)

Scott Gottlieb was a very different FDA Commissioner; Alex Azar is a very different Secretary of HHS

BOTH SEE/SAW COMPETITION AS THE SOURCE OF INNOVATION IN THE US

Building on the success of generics, and creating the same kind of success with biosimilars, will require not just efficient approval to enter the market, but also payment systems that can harness new competition. So I want to talk about both elements of a successful generic and biosimilars market today: ***our efforts at the FDA to foster competition through efficient, safe approvals, and our efforts to create the right incentives, and remove any wrong incentives, to support that competition.***

Alex M. Azar II

Association for Accessible Medicines 6Feb19[1]

According to Azar, "Those Against Biosimilars are, Simply, on the Wrong Side of History“ [1,2] But we have yet to see Administration Policies to match these apparent intentions to enable biosimilars to prosper in the US. Yet some of the answers are already available[3]

- https://www.hhs.gov/about/leadership/secretary/speeches/2019-speeches/remarks-to-the-association-for-accessible-medicines.html
- https://www.centerforbiosimilars.com/conferences/aam-access-2019/according-to-azar-those-against-biosimilars-are-simply-on-the-wrong-side-of-history
- https://www.biosimilardevelopment.com/doc/a-second-reformation-returning-biosimilar-regulations-to-scientific-roots-0001

Follow-Up Questions?

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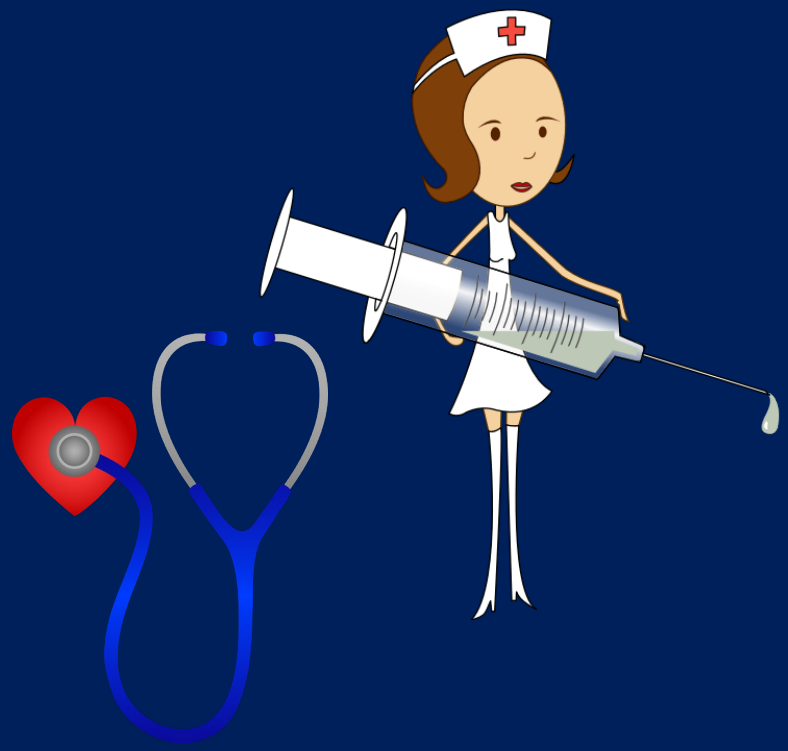
Biosimilars in the Real-World: Patient and Provider Perspectives



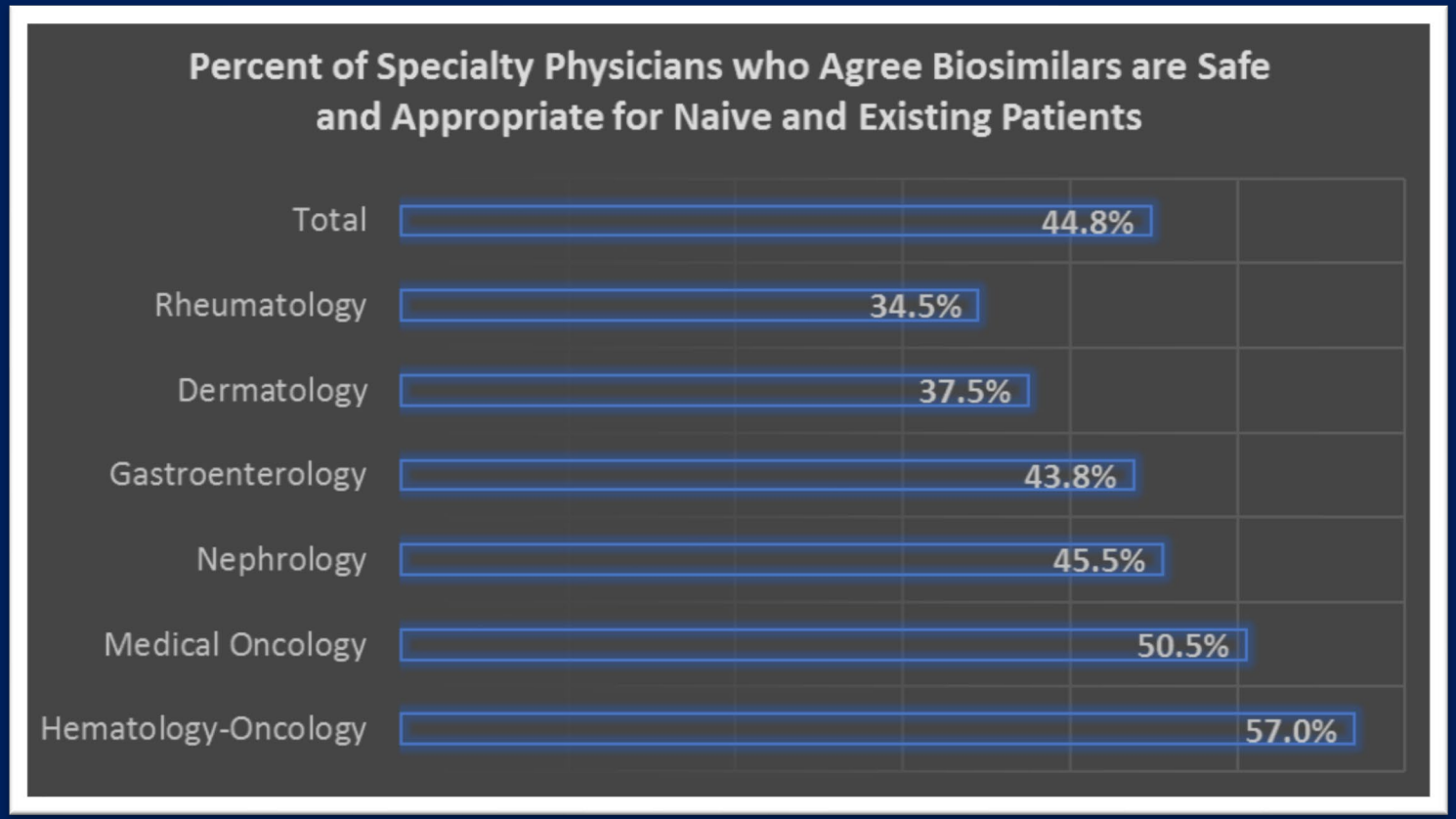
Who are the stakeholders for biosimilars in the United States?

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

Factors Influencing 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….



Cohen et al. *Adv Ther* 2017;12(2):2160-2172.

Factors Influencing 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

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

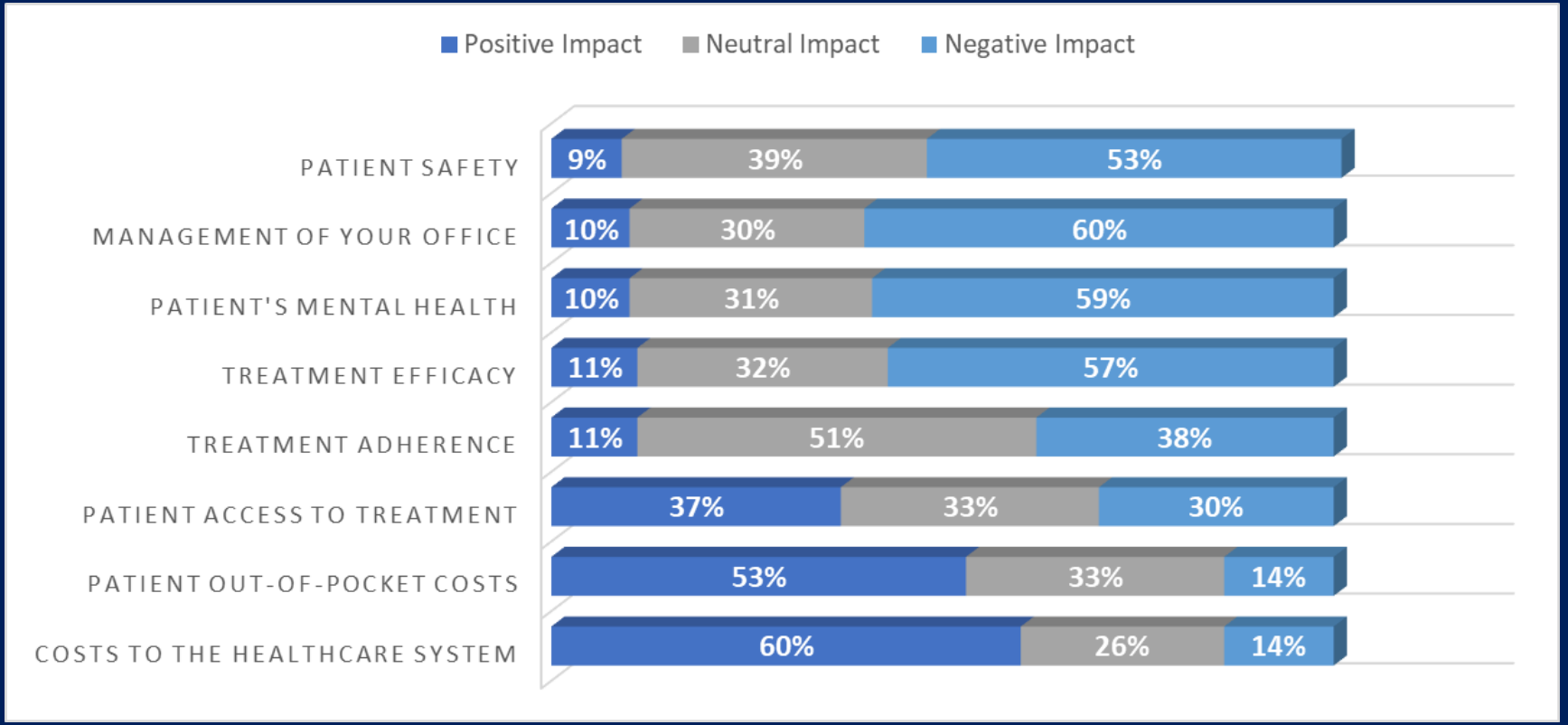
Teeple et al. *Curr Med Res Opin* 2019;35(4):611-617.

Factors Influencing Biosimilar Utilization

Uncertainty - Prescribers

- **When asked about the impact of non-medical switching**

67% of surveyed physicians had not heard the specific term “non-medical switching”



Adapted from: Teeple et al. *Curr Med Res Opin* 2019;35(4):611-617.

Factors Influencing Biosimilar Utilization

Uncertainty - Prescribers

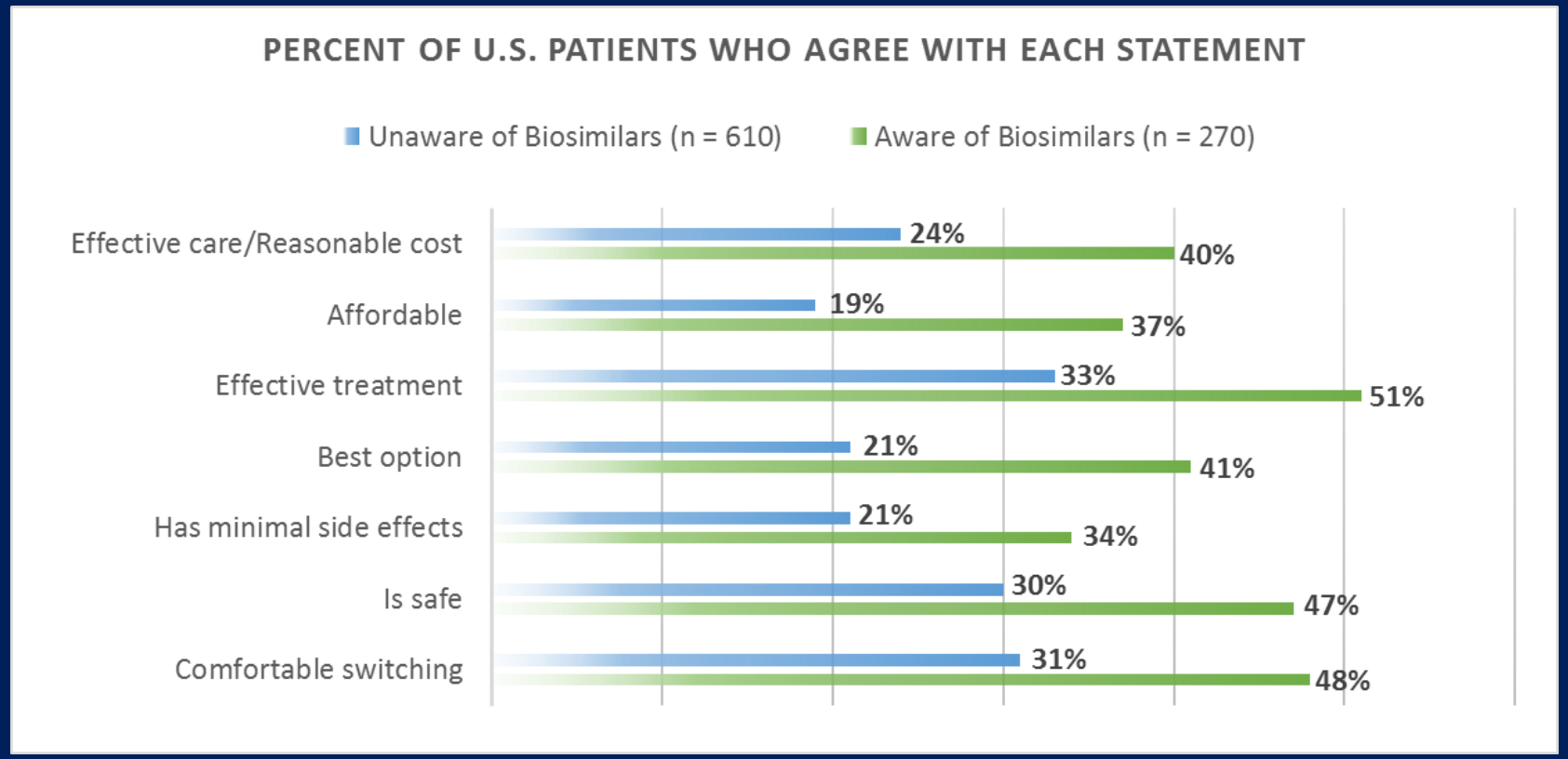
Leonard et al. **Factors affecting health care provider knowledge and acceptance of biosimilar medicines: a systematic review**. *J Manag Care Spec Pharm 2019;25(1):102-112.*

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 are unsure

Factors Influencing Biosimilar Utilization

Uncertainty - Patients



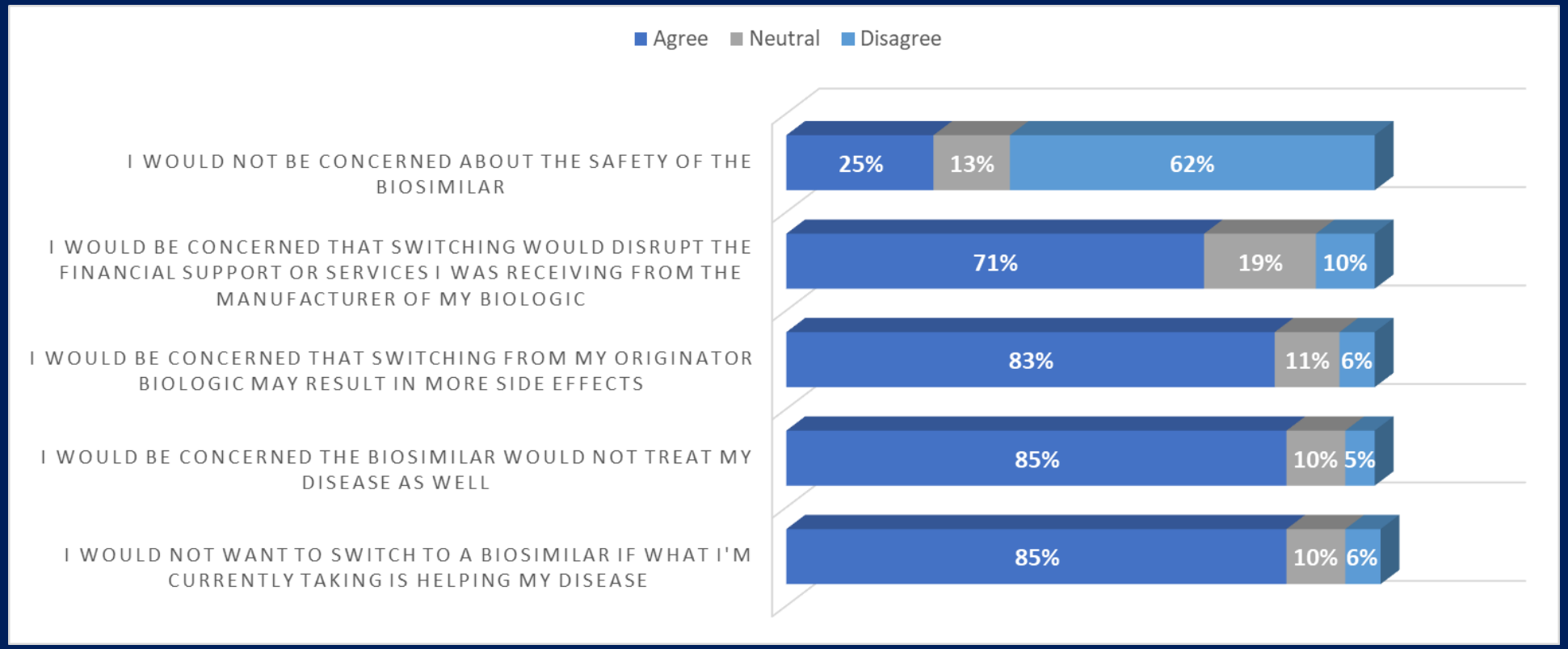
- Basic awareness = Defined as reporting at least a general impression of biologics or knew the term “biologic” or “biosimilars”.

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

Factors Influencing Biosimilar Utilization

Uncertainty - Patients

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



Adapted from: Teeple et al. *Curr Med Res Opin* 2019;35(4):603-609.

Factors Influencing Biosimilar Utilization

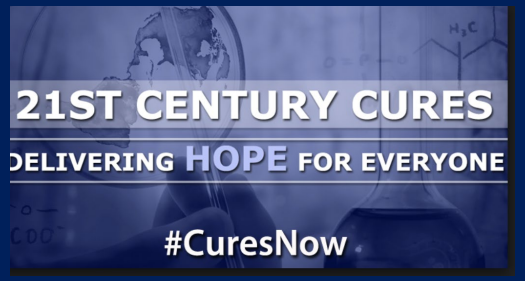
Uncertainty - Patients

….and other studies

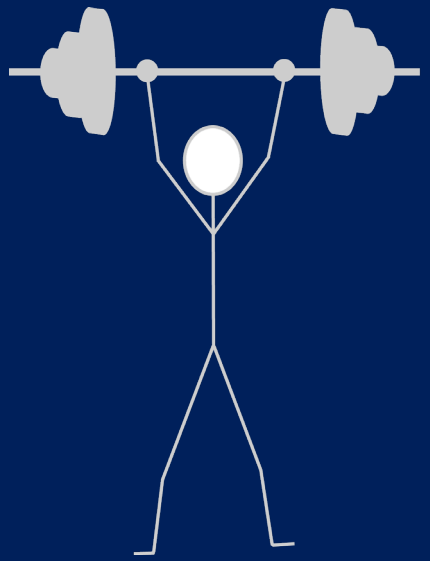
Post-approval studies evaluating comparative safety and effectiveness are critical to generating real-world evidence to inform clinical practice and policy decisions

OPPORTUNITY FOR EDUCATION

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

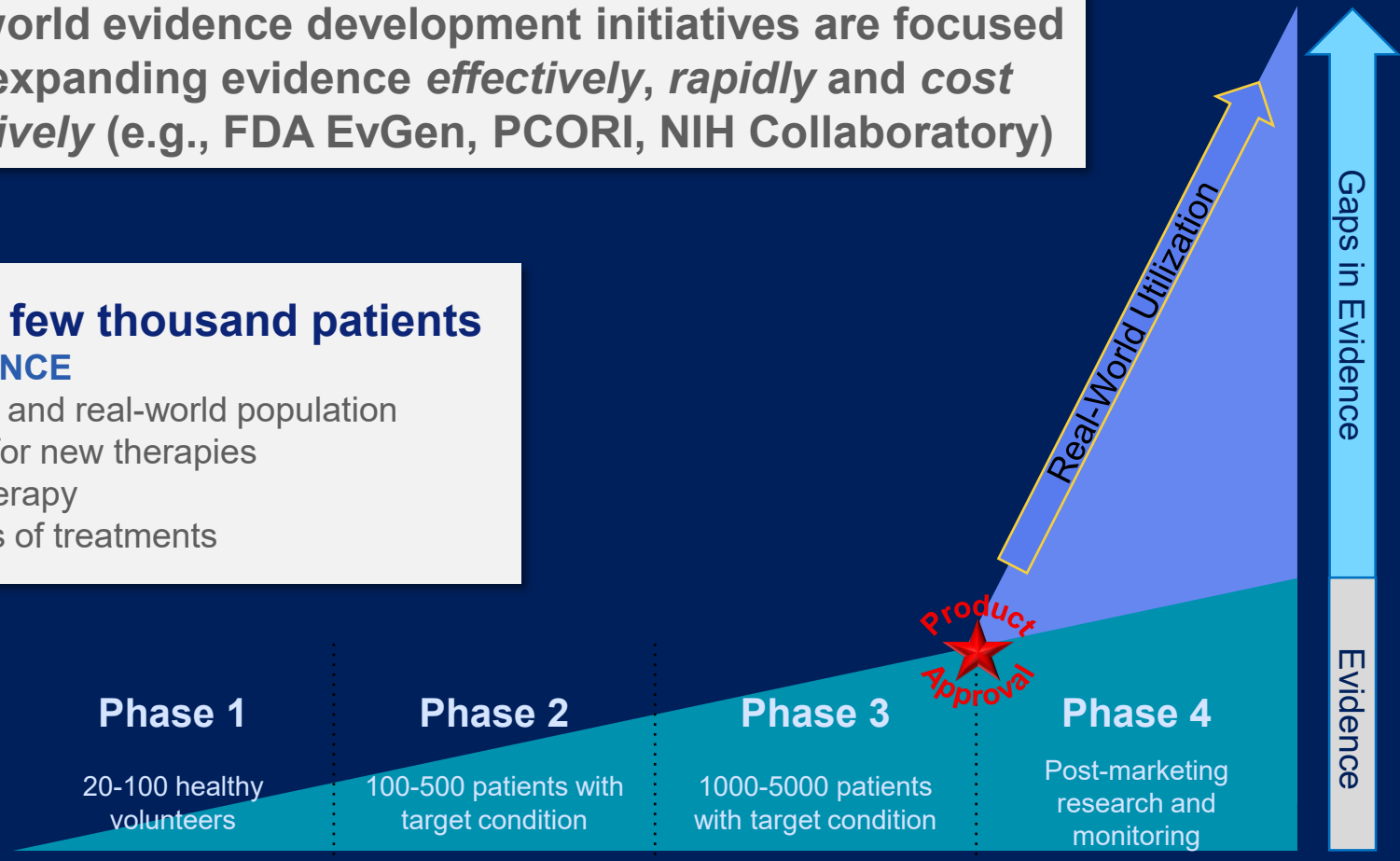
Origins in the Gap in Evidence

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



Real-world utilization quickly outpaces available clinical evidence

Real-World Data Sources

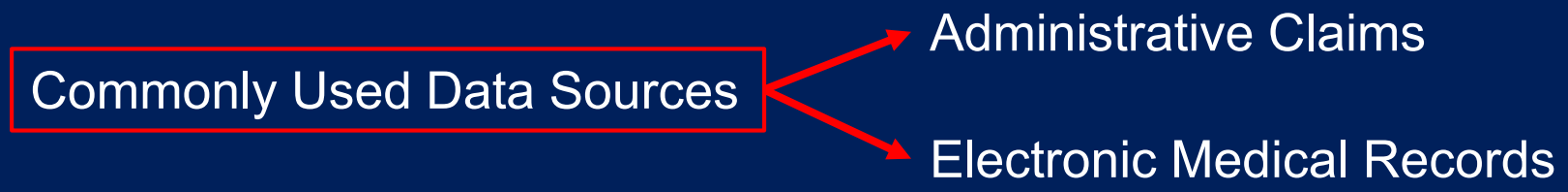
Study Types

- 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

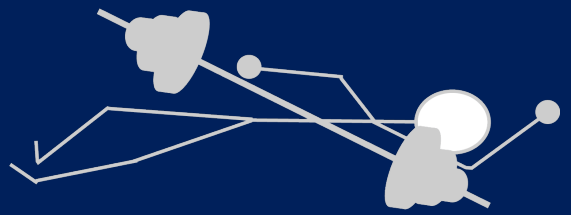
Why is data collected?

- Payment/billing
- Document clinical care
- Physician decision support
- Recordkeeping
- Registries
- 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 Data - Limitations

- Data are 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…

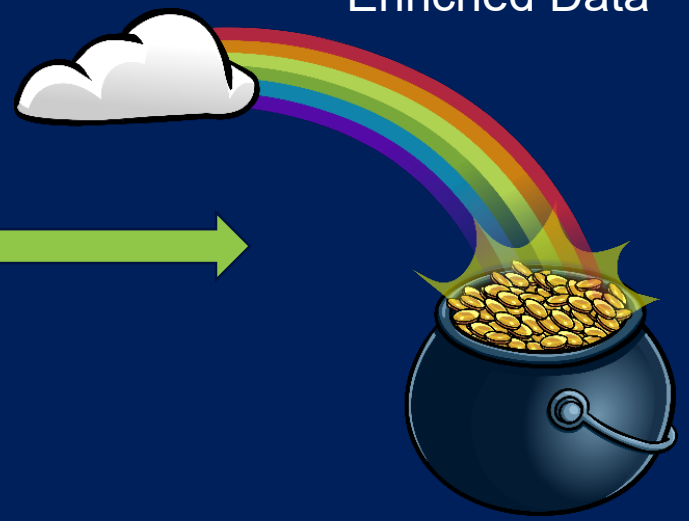
- Wearable devices
- Mobile phone applications
- Social Media

- Mobile app Social Media

LINK

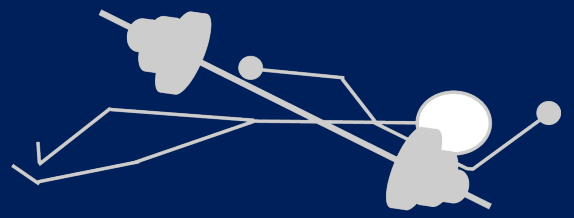
- Electronic Health Record
- Administrative Claims

- Enriched Data



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



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

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 Lines of Inquiry To Date

Data fitness / infrastructure

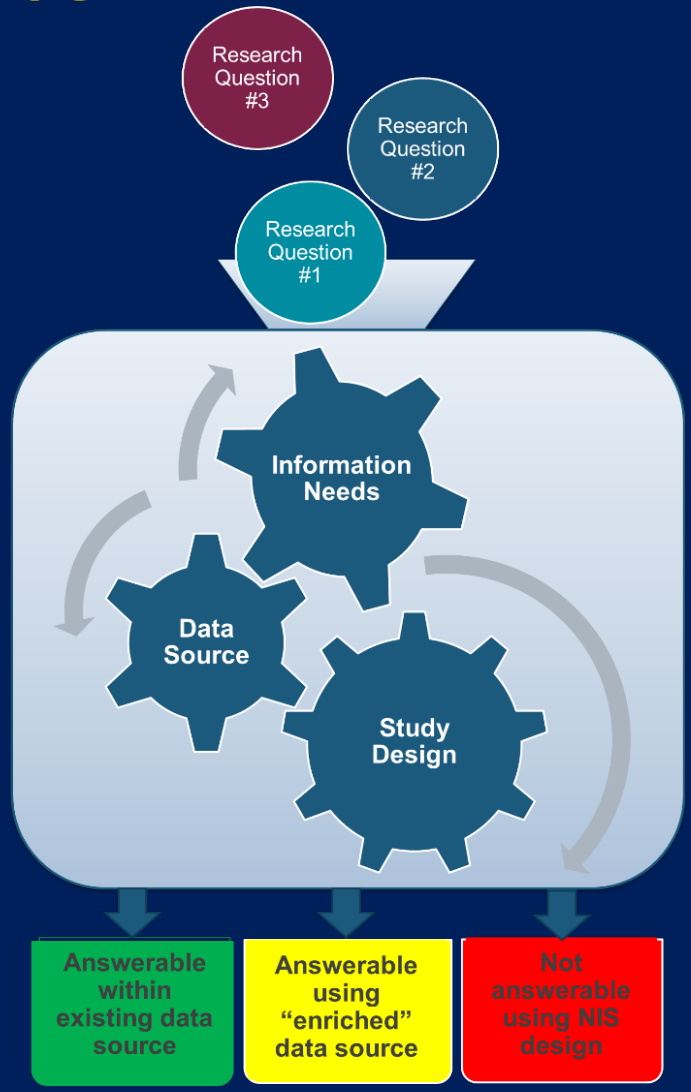
- Data availability and characterization
  - Capture of NDC information on medical claims
- Impact of transition from ICD-9 to ICD-10, claims-based algorithms

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 Research - Manuscripts

Desai RJ, Kim SC, Curtis JR, et al. **Methodologic Considerations for Noninterventional Studies of Switching from Reference Biologic to Biosimilars.** *Pharmacoepidemiol Drug Saf.* 2019:1-13. Epub ahead of print. https://onlinelibrary.wiley.com/doi/full/10.1002/pds.4809

Lockhart CM, McDermott CL, Felix T, et al. **Barriers and Facilitators to Conduct High-Quality, Large-Scale Safety and Comparative Effectiveness Research: The Biologics and Biosimilars Collective Intelligence Consortium Experience.** *Pharmacoepidemiol Drug Saf.* 2019:1-3. Epub ahead of print. https://onlinelibrary.wiley.com/doi/full/10.1002/pds.4885

McMahill-Walraven CN, Kent DJ, Panozzo CA, et al. **Harnessing the Biologicis and Biosimilars Collective Intelligence Consortium to Evaluate Patterns of Care**. *J Manag Care Spec Pharm.* Published online August 2019. https://www.jmcp.org/doi/abs/10.18553/jmcp.2019.19041

Kent DJ McMahill-Walraven CN, Panozzo CA, et al. **Descriptive Analysis of Long- and Intermediate-Acting Insulin and Key Safety Outcomes in Adults with Type 2 Diabetes Mellitus.** *J Manag Care Spec Pharm.* Published online August 2019. https://www.jmcp.org/doi/abs/10.18553/jmcp.2019.19042

BBCIC – Current Projects

COMPARATIVE EFFECTIVENESS RESEARCH – G-CSFs

The BBCIC has started our FIRST formal Comparative Safety and Effectiveness study of granulocyte-colony stimulating factors (filgrastim, pegfilgrastim) between the originator biologics and their available biosimilars.

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. Currenty 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 Comparateive Effectiveness Research (CER) project focused on G-CSFs.

BBCIC – Current Projects

ONCOLOGY FEASIBILITY AND DATA FITNESS

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.

Follow-Up Questions?

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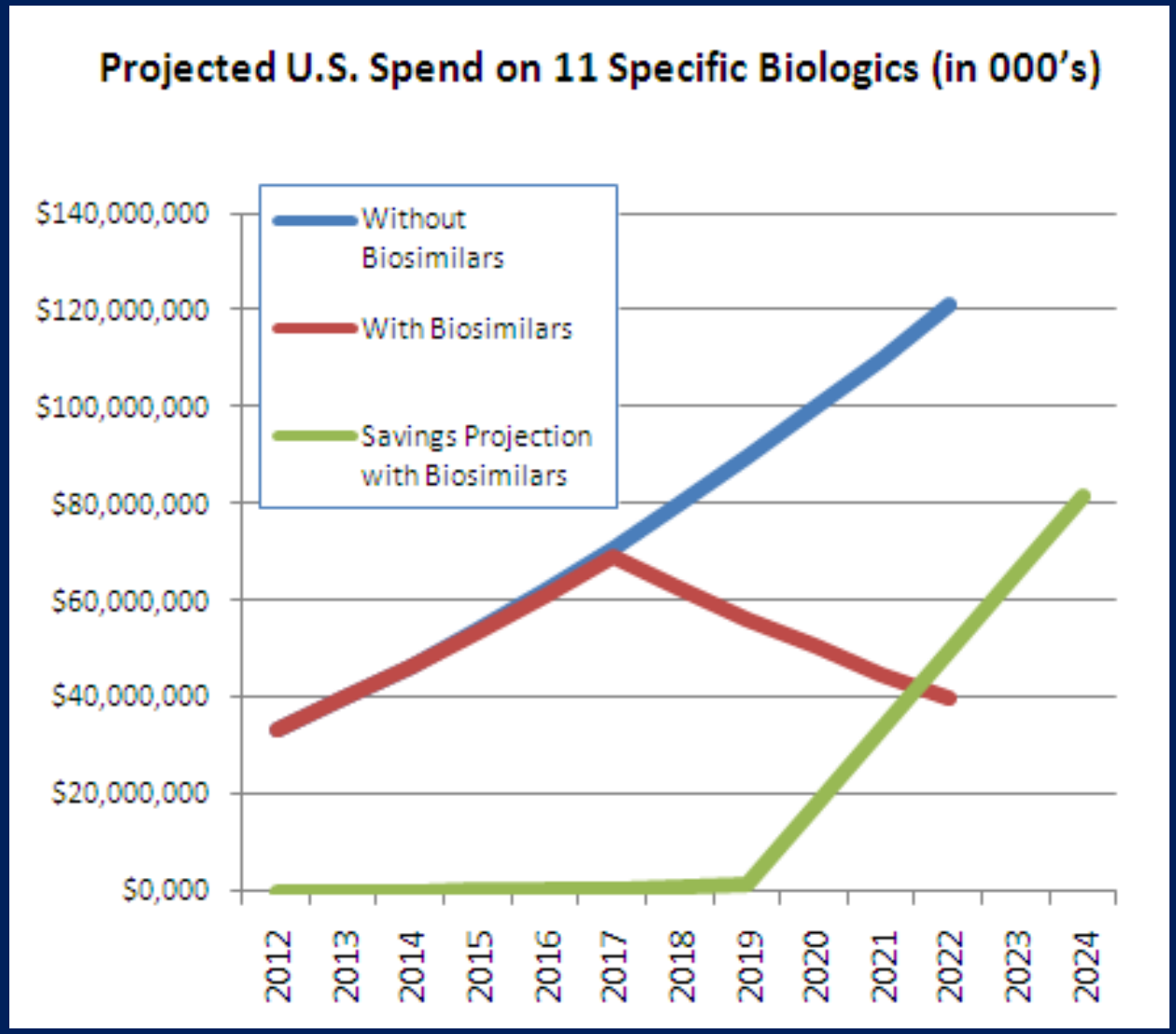
Biosimilars in Practice-The Yale New Haven Health System Experience

Yale New Haven Health At-a-Glance

- Five Hospitals
  - Yale New Haven Hospital
  - Bridgeport Hospital
  - Greenwich Hospital
  - Lawrence + Memorial Hospital
  - Westerly Hospital
- 2,563 Licensed Beds

- 340B and non-340B hospitals
- Founding Member and Service Provider to the Northeast Purchasing Coalition (NPC)
  - 14 Members
  - Aggregation contracting and utilization projects

What We Originally Thought



Steve Miller, The $250 Billion Potential of Biosimilars, Express Scripts Int'l (Apr. 23, 2013).

YNHHS Take 1-Tbo-Filgrastim (Granix®)

- BLA 351(a) approval pathway
- Biosimilar in European Union
- Only applied for 1 FDA indication and not all of filgrastim indications
- At the time No indication for
  - BMT
  - Stem Cell Mobilization
  - AML

YNHHS: Recommended filgrastim and tbo-filgrastim therapeutically equivalent

- Approval: Therapeutic equivalence except in pediatric patients, BMT patients and mobilization in donors
- Limited or no data in these populations

Concerns from Prescribers

- Desire for clinical studies
- Immunogenicity
- Limited understanding or comfort level with regulatory requirements/process
- Patient Preference
- Cost-savings not worth the conversion

YNHHS Take 2: Create Overall Strategy for Biosimilars

- Identified the need to set a precedent for the management of all future Biosimilars
  - Goal to declare therapeutic equivalence for all biosimilars
- Identified and met with Key Stakeholders
- Identified the Oncology Chief Medical Officer as the project Sponsor
- Standardized presentation and recommendation presented to all local P&T Committees, Medical Executive Committees and YNHHS Formulary Integration Committee (FIC)
- Recommendation presented to the YNNHS Oncology Subcommittee and at Oncology Grand Rounds
  - One-on-One stakeholder discussions occurred as needed

Key Points in Adoption of Biosimilars

We are already using "biosimilars"

Drugs with significant changes in manufacturing process

- Insulin
- Darbepoetin
- Immune Globulin
- Vaccines
- Many Biologics

Table Number of Changes in the Manufacturing Process Reported by the European Medicines Agency After Drug Approval by the FDA, Through 2012

Drug	Process changes since approved, N
Infliximab (Remicade)	36
Etanercept (Enbrel)	21
Adalimumab (Humira)	18
Abatacept (Orencia)	7
Golimumab (Simponi)	2

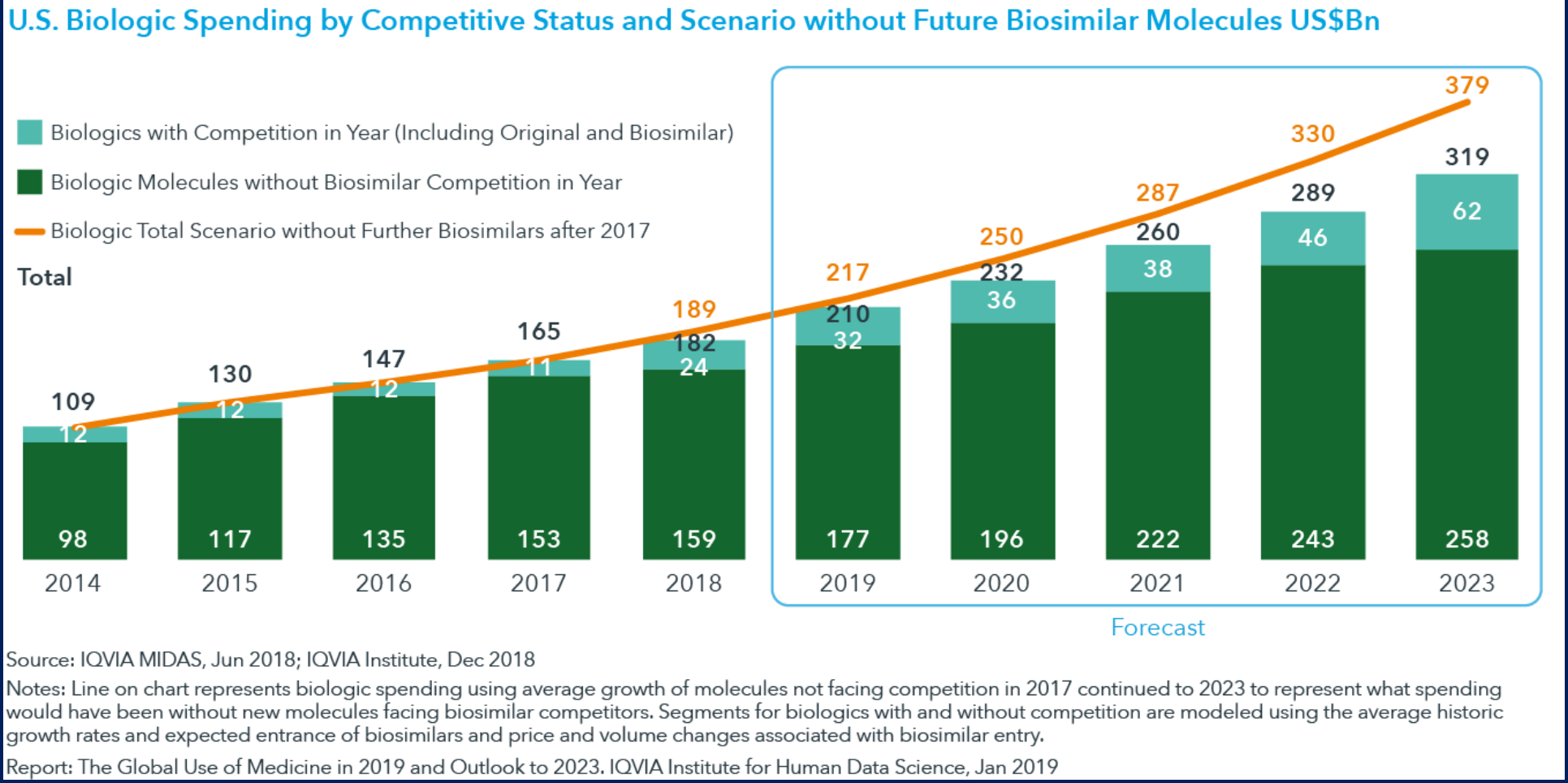
FDA indicates US Food and Drug Administration.
Source: Schneider CK. *Ann Rheum Dis*. 2013;72:315-318.

Am Health Drug Benefits.2016;9(9):515-518

YNHHS Formulary Biosimilar Decision/Policy

- Biosimilars are considered therapeutically equivalent to the reference drug for the FDA approved indications
- Formulary decisions based on cost and operational considerations
- Pharmacy to communicate with key stakeholders prior to formulary switch
- Option to request a formal review
  - *Must provide additional evidence to support request*

What We Are Actually Experiencing



Source: IQVIA MIDAS, Jun 2018; IQVIA Institute, Dec 2018

Notes: Line on chart represents biologic spending using average growth of molecules not facing competition in 2017 continued to 2023 to represent what spending would have been without new molecules facing biosimilar competitors. Segments for biologics with and without competition are modeled using the average historic growth rates and expected entrance of biosimilars and price and volume changes associated with biosimilar entry.

Report: The Global Use of Medicine in 2019 and Outlook to 2023. IQVIA Institute for Human Data Science, Jan 2019

YNHHS/NPC Biosimilar Adoption

NPC contracts: filgrastim, infliximab and pegfilgrastim biosimilars

- 100% adoption of filgrastim-sndz (99% Market Share)
- 100% adoption of pegfilgrastim-cbqv
- 65% adoption of infliximab-abda and infliximab-dyyb

- No current contract for epoetin alfa-epbx

OPINION | LETTERS

We Need a More Rational Biosimilars Policy

Throwing in the towel on a whole new category of medicines, just shy of a decade in, is not only shortsighted, it's bad for patients and provider choice.

There are more than 500 biosimilars in the pipeline. Rebate-driven insurance requirements specifying which companies' biosimilar drugs are covered will significantly encumber the complex systems of checks used to prevent tragic medication errors. For intravenous chemotherapy, 57 checks are performed.

As of June, trastuzumab, used for breast cancer, has five biosimilars, and pegfilgrastim, used to prevent life-threatening infections in cancer patients, has two biosimilars.

By using rebates, each of the eight companies which make these two drugs can secure insurer-preferred status creating a new paradigm for treatment. Besides prescribing the most effective chemotherapy regimen, physicians will need to verify that the drugs are correct based on the patient's insurance. For these two drugs, cancer clinics will need to stock 11 products (with varying amounts per vial) versus four, increasing the risk of mix-ups since biosimilars look-alike. Clinicians will need to ensure insurance-specific drugs are prepared, dispensed and administered correctly. If the clinic doesn't have the required drugs available, treatment will be delayed, which with pegfilgrastim can be life-threatening.

Imagine four people ordering steak at a restaurant requiring that each steak is sourced from a different beef producer as a condition of paying for the meal. Rebate-driven insurance requirements by drug manufacturers not only increase health-care costs; they also increase the risk of harm to vulnerable patients

Rita Shane, Pharm.D.

Shane, R, *WSJ*. August 27, 2019.

Profit and Loss (P&L) Analysis

- Need to collaborate with your Revenue Reporting Department
- Analysis Requires:
  - Drug: CPT codes, contract cost, common dose, pass-through status
    Utilization: billed units by payer
  - Payer contracts
- Decreased drug spend is not always an overall win for the organization

Infliximab vs. Pegfilgrastim: YNHHS P&L

Drug	Spend	Net Revenue	P&L
Infliximab			
Infliximab	↑	↑	↑
Infliximab-dyyb	↓	↓	↓
Infliximab-abda	↓	↓	↓
Pegfilgrastim			
Pegfilgrastim	↑	≈	↓
Pegfilgrastim-jmdb	↓	≈	≈
Pegfilgrastim-cbqv	↓	≈	≈

What are the Barriers to Realizing the Value?

- Acceptance by patients and providers
  - Need for continued education on the FDA approval process and standards
  - Positions of physician organizations
- On-going litigation by the innovator manufacturers
- Design of innovator novel delivery technologies
- Reimbursement
- Current Formulary Management Model

What is next for YNHHS?

POST-TEST

LQ1: Of the 23 biosimilars that have been approved in the U.S. to date, how many are available on the market?

a) 4
b) 9
c) 17
d) 23

LQ1: Of the 23 biosimilars that have been approved in the U.S. to date, how many are available on the market?

a) 4
b) 9 (slide 11)
c) 17
d) 23

LQ2: Among U.S. prescribers in specialties where biologics are frequently prescribed, what is the percent who trust biosimilars are safe?

a) Between 10% and 20%
b) Between 40% and 50%
c) Between 60% and 70%
d) Between 80% and 90%

LQ2: Among U.S. prescribers in specialties where biologics are frequently prescribed, what is the percent who trust biosimilars are safe?

a) Between 10% and 20%
b) Between 40% and 50% (slide 32)
c) Between 60% and 70%
d) Between 80% and 90%

LQ3: All of the following are limitations of commonly-used real-world data sources, EXCEPT:

a) Data are typically collected for reasons other than research
b) Market uptake may influence research capabilities
c) Clinical effectiveness outcomes may be challenging to identify
d) Data are usually randomized

LQ3: All of the following are limitations of commonly-used real-world data sources, EXCEPT:

a) Data are typically collected for reasons other than research
b) Market uptake may influence research capabilities
c) Clinical effectiveness outcomes may be challenging to identify
d) Data are usually randomized (slide 42)

LQ4: Which is a barrier to biosimilar adoption within a hospital system?

a) Ongoing litigation prevents access to biosimilars
b) Uncertainty around reimbursement
c) Design of novel delivery technology
d) Both a and b
e) All of the above

LQ4: What is a barrier to biosimilar adoption within a hospital system?

a) Ongoing litigation prevents access to biosimilars
b) Uncertainty around reimbursement
c) Design of novel delivery technology
d) Both a and b
e) All of the above (slide 64)

Questions?

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