Biosimilars Action Plan Scorecard

Is FDA helping Adoption?

4 November 2019, 3:30-4:30pm

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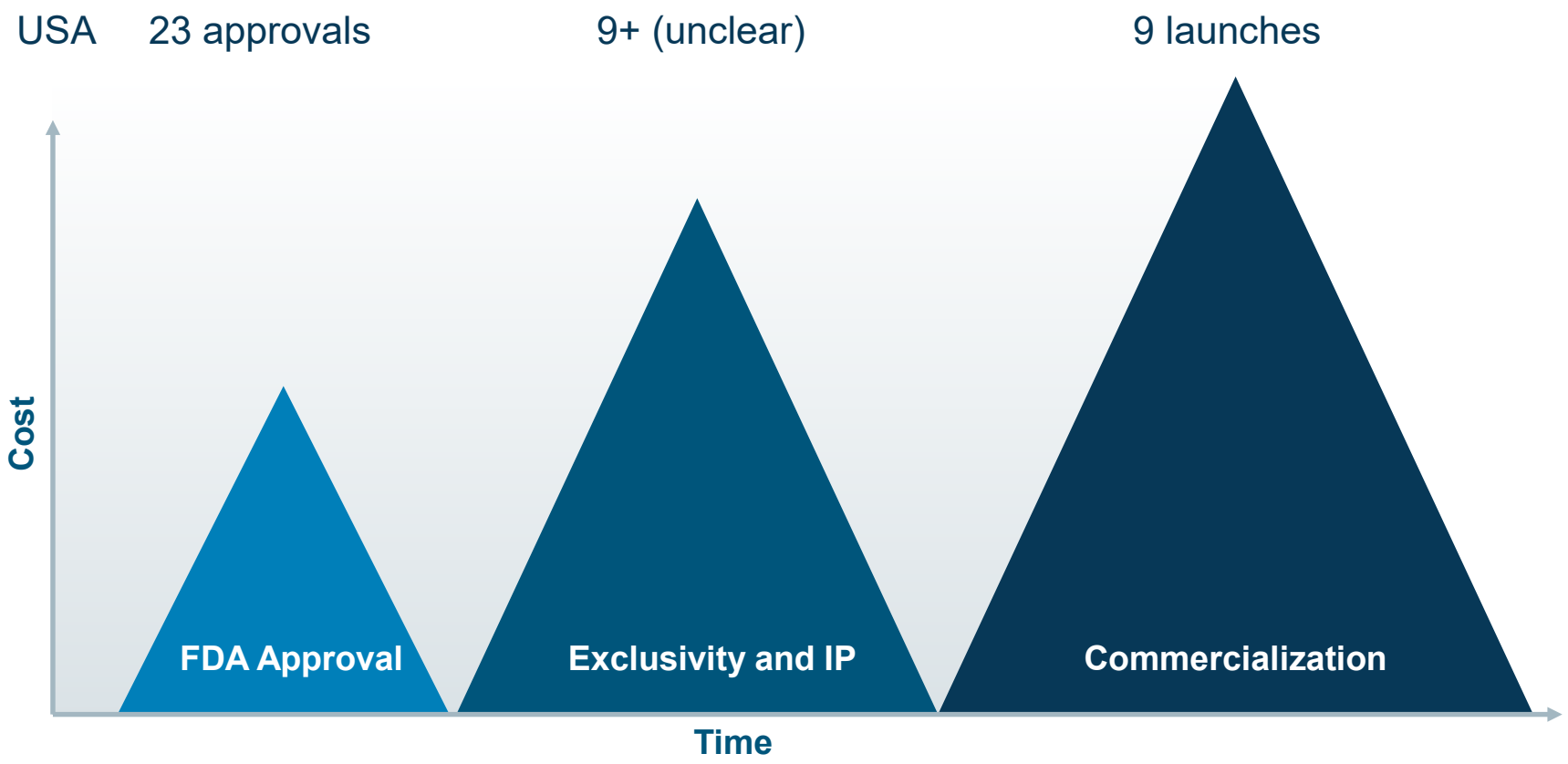
Avalere Health | An Inovalon Company

The Mountainous Challenges for Biosimilars in the US

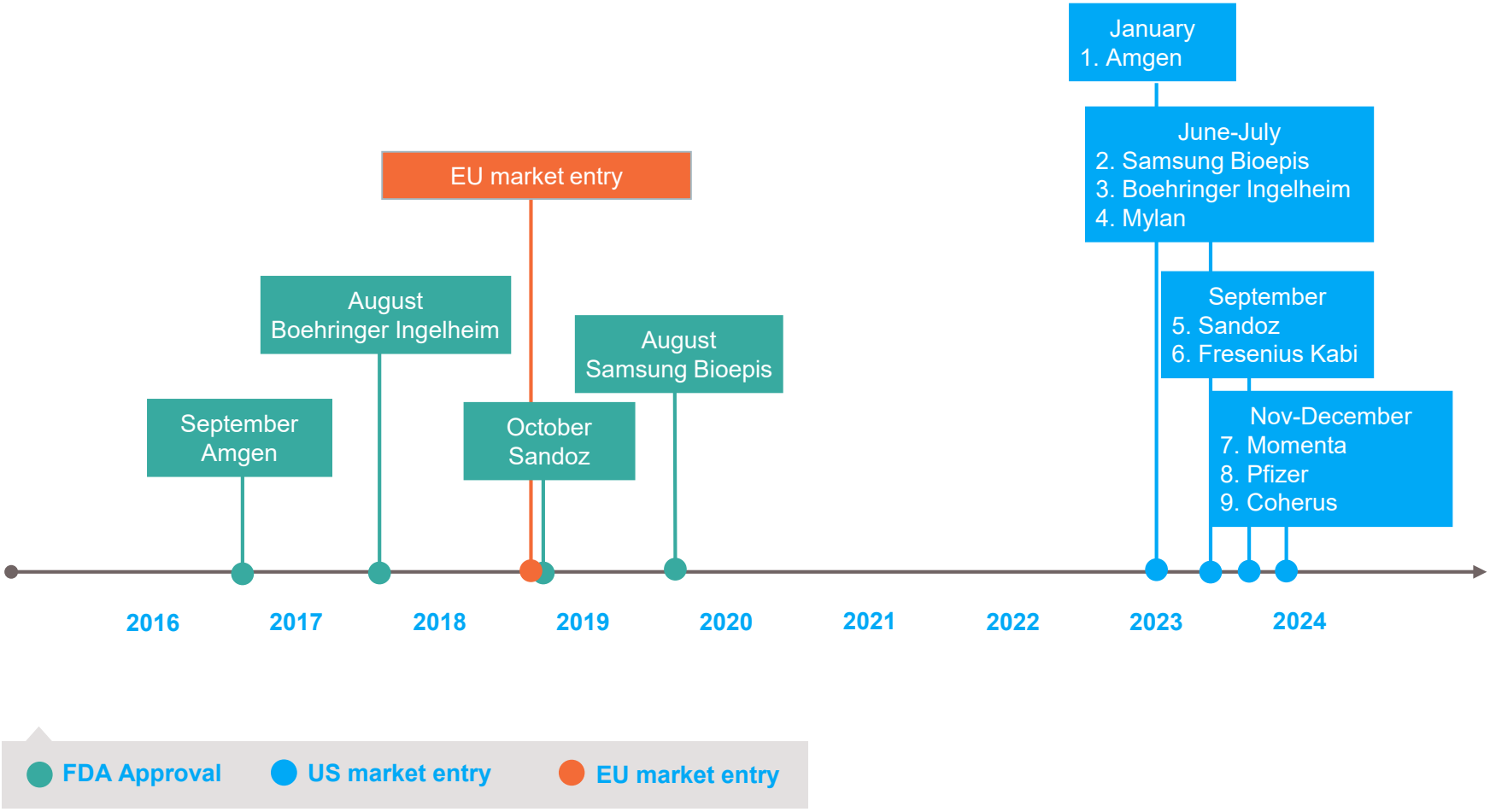
FDA approval is the first of a series of challenges



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

FDA Approval is Only the First Step

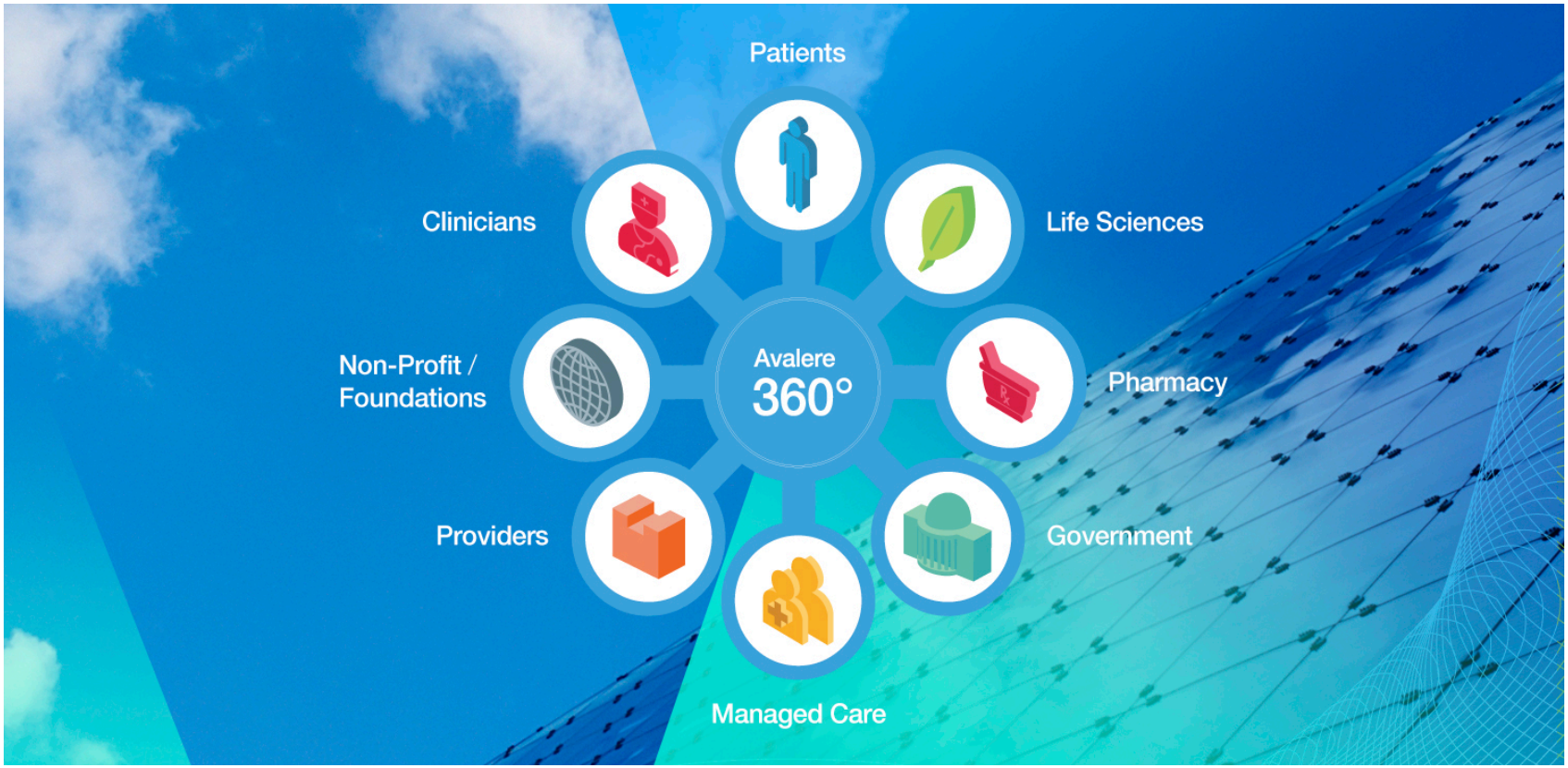
Example: AbbVie's US Humira® (adalimumab)



1 https://neuclone.com/abbvies-us-humira-monopoly-four-years-and-60-billion-of-additional-sales-protection/ (accessed 3Jun19)

Product Development is no Longer Compartmentalizable

THERE IS A CACOPHANY OF STAKEHOLDER VOICES AND OPINIONS TO CONSIDER



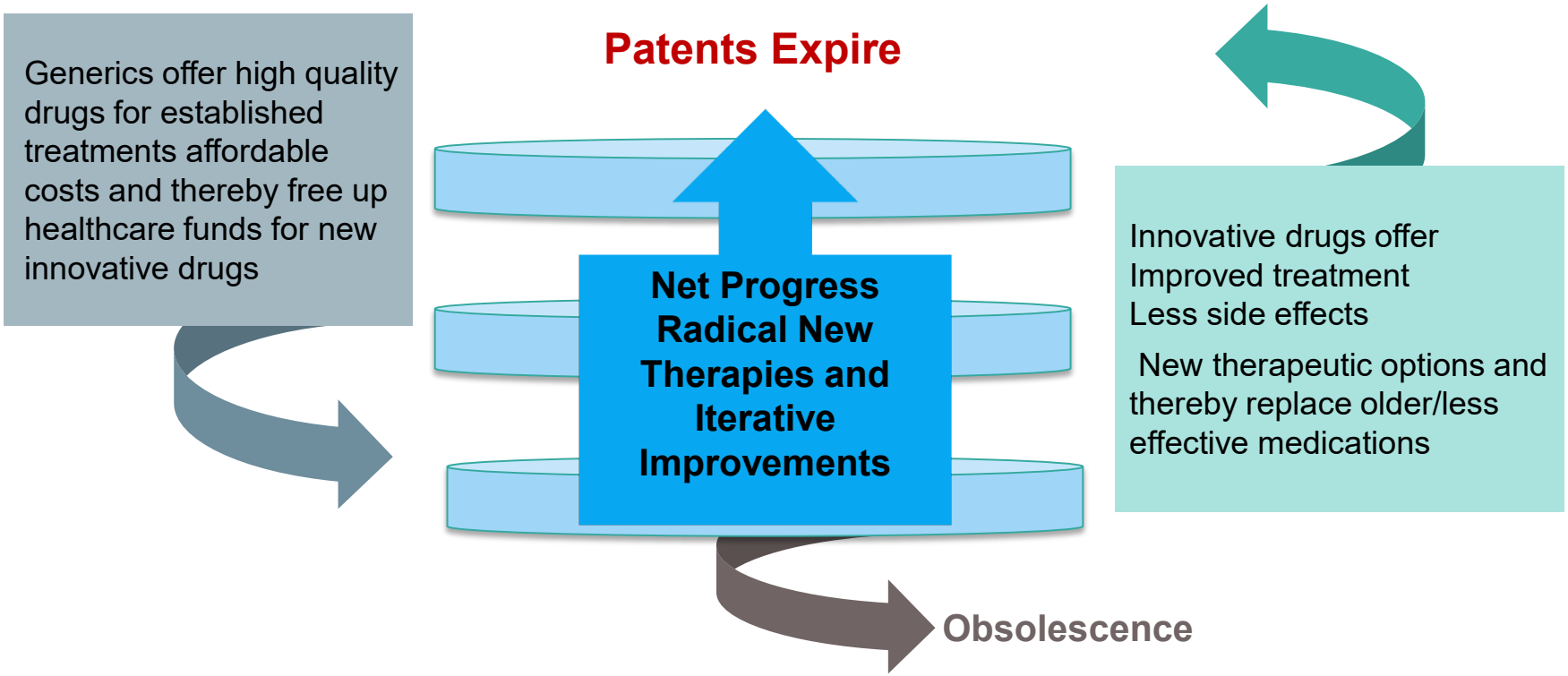
THOUGHTFUL VOICES ARE NOT ALWAYS THE LOUDEST

Outline

- **Context**
  - FDA is simply the first challenge for US Biosimilars
  - High expectations for substantial savings through competition
  - The future of biotech depends on getting biosimilars right
- FDA's Biosimilar Action Plan
  - Recap – Biosimilars are biologics we know a lot about
  - The Reference Product Matters – simply solved
  - Switching Frees the Market, but does Interchangeability matter?
- Conclusions

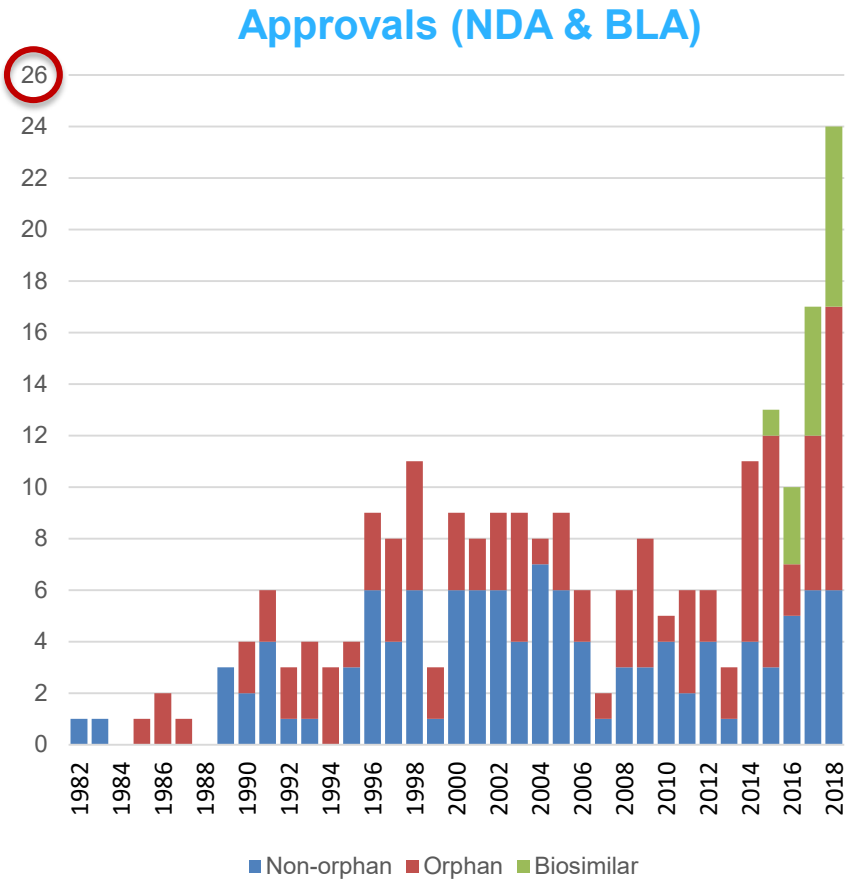
The Expectation: Generics Are Products of the Same Quality with the Same Clinical Value at a Lower Price

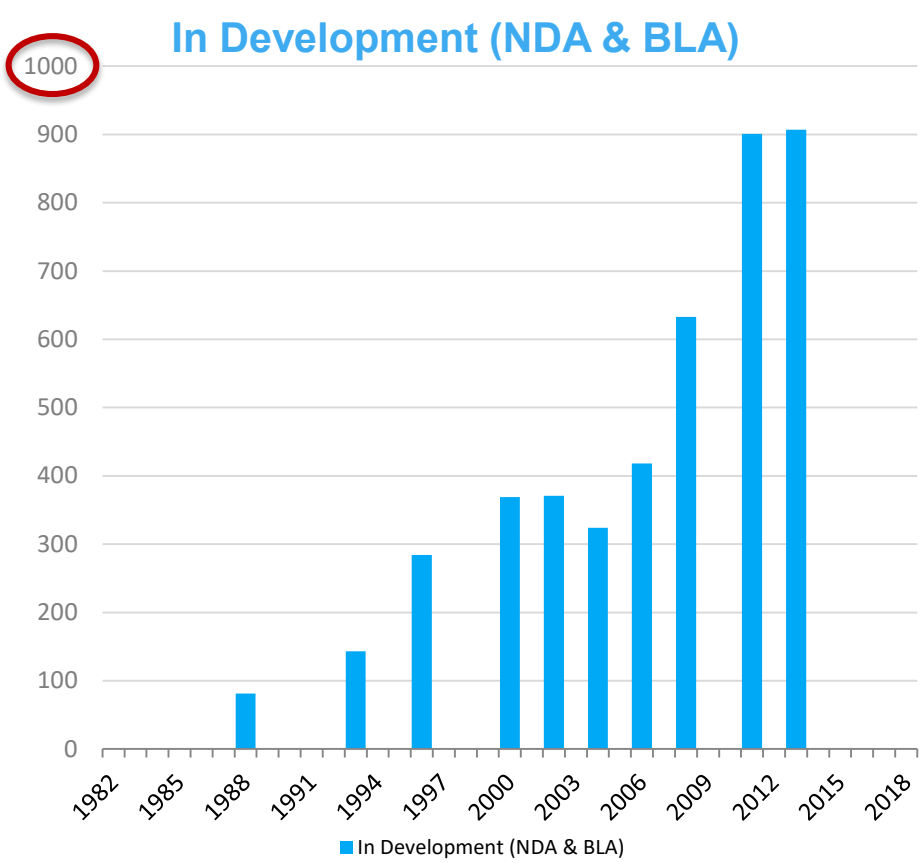
INNOVATION IS DRIVEN BY COMPETITION



Biosimilars are expected to offer the same value at a lower cost than branded biologics, and follow the generic precedent

Biotech Approvals Have Increased and are Expected to Rise





As medicines in development move through the pipeline, the expansion of the biologics market is expected to dramatically increase

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

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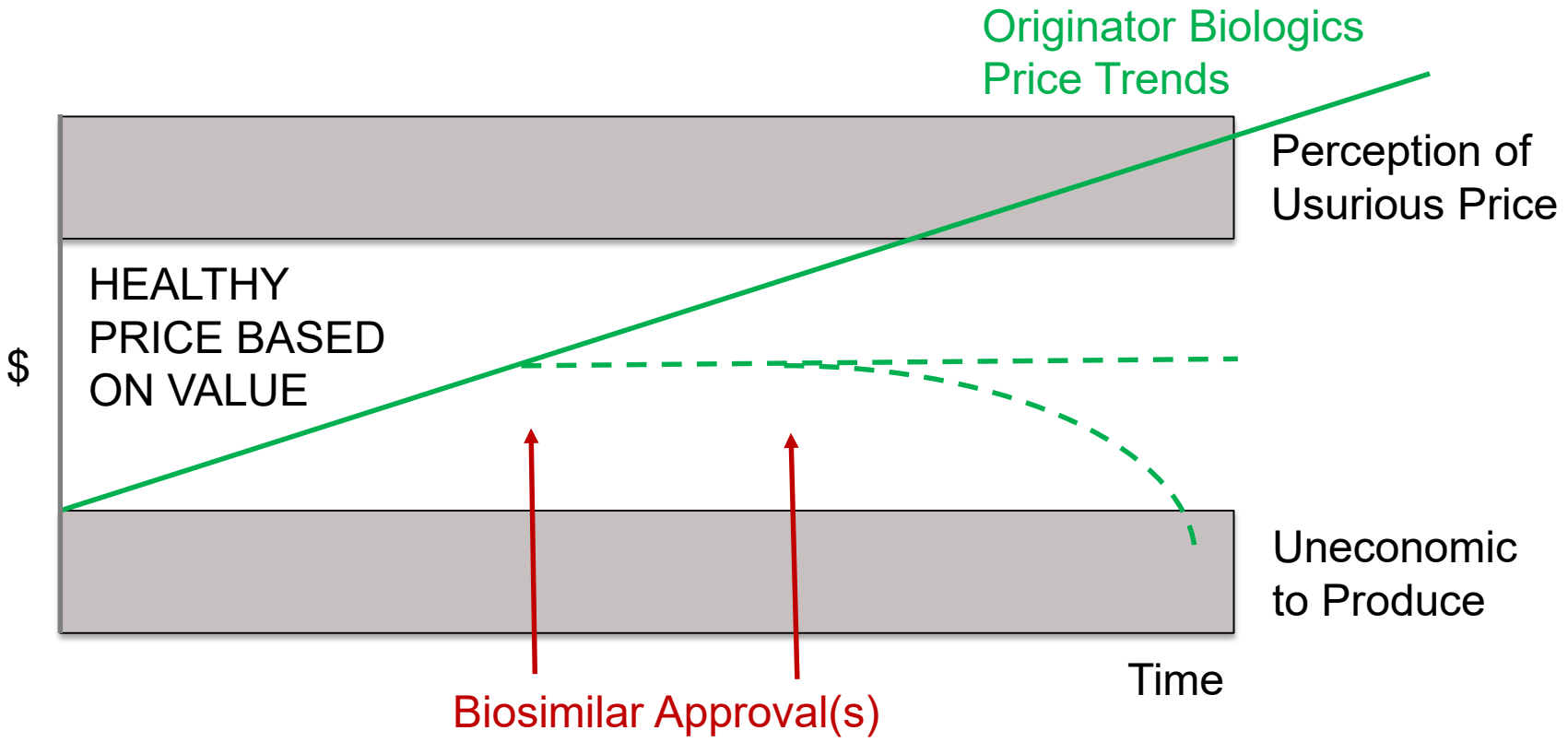
Context: Public Recognition of Value of Biopharmaceuticals

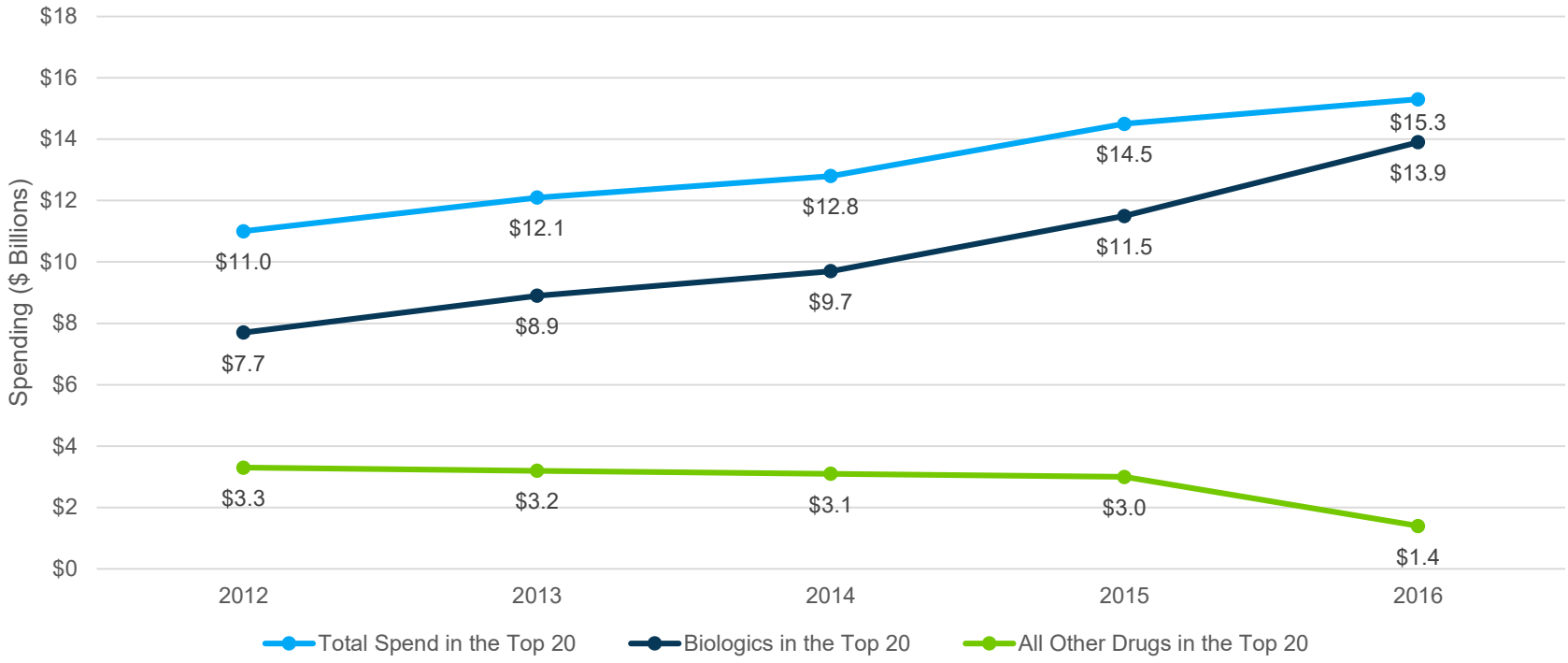
VALUE IS A COMBINATION OF CLINICAL OUTCOME AND PRICE



Need mechanisms 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.

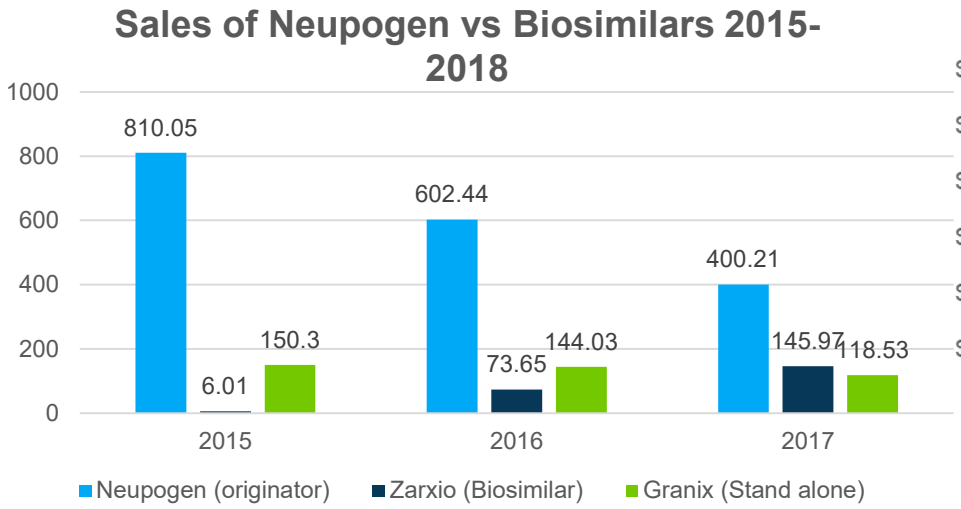
Example: Filgrastim

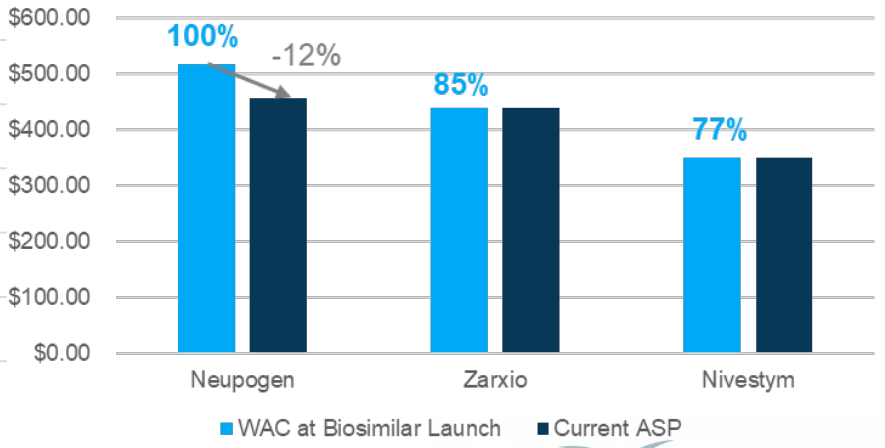
Biosimilar Competition /

Product	Company	Launch	Market Share ('18)[1]
Neupogen	Amgen	1991	48%
Zarxio	Sandoz	2015	31.7%
Nivestym	Pfizer	2018	N/A
Granix**	Teva	2012	20.3%

**Granix was approved as a351(a) standalone

- Reference price was reduced upon biosimilar entry
- Second biosimilar entering (Nivestym late 2018), leading to further changes
- Limited cost savings for the patient as cost per-patient is virtually the same between biosimilars and the originator[2]
- Need to also consider PegFilgrastims and devices





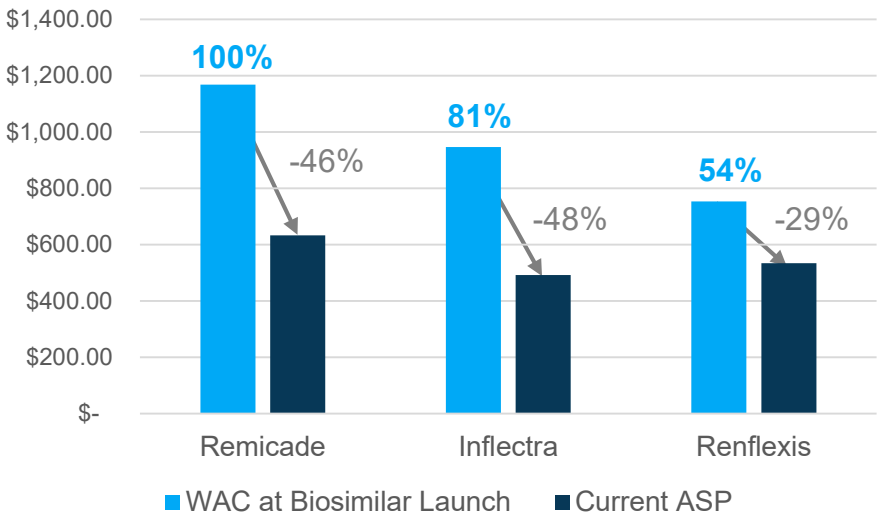
Note. WACs and ASPs for 480 mcg formulation

1. https://www.journalofclinicalpathways.com/news/iqvia-data-show-biosimilars-struggling-market-share-us
2. https://www.managedcaremag.com/archives/2019/1/neupogen-biosimilars-end-tie-loss-biosimilars
3. https://www.statista.com/statistics/869910/neupogen-sales-loss-to-biosimilars/

Example: Infliximab

Biosimilar Competition /

Product	Company	Launch	2018 Sales (M)	Market Share
Remicade	Janssen	1998	$3,664	93.8%
Inflectra	Pfizer	2016	$259	5.3%
Renflexis	Merck	2017	$36*	1.0%



- Biosimilars have an impact on price of the reference product
- Market share remains with the originator
- This does not create sustainability for individual products or collectively to the US specialty market
- This is not a “generic” model or a “brand” model – it is NEW

No clear commercial model for biosimilars – savings with out market share is not sustainable

*Merck did not report sales for Renflexis in their 10K statements, so cost was calculated assuming Renflexis has 1% of the market share per IQVIA.[1]
TNF: Tumor necrosis factor; WAC: Wholesale Acquisition Cost; ASP: Average Sales Price; MM: Managed Medicaid; PAP: Patient Assistance Program

1. https://medecon.org/wp-content/uploads/2019/07/BiosimilarsCompetition_F.pdf

Europe is Succeeding... US apparently not...

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 U.S. 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...

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

The Mountainous Challenges for Biosimilars in the US

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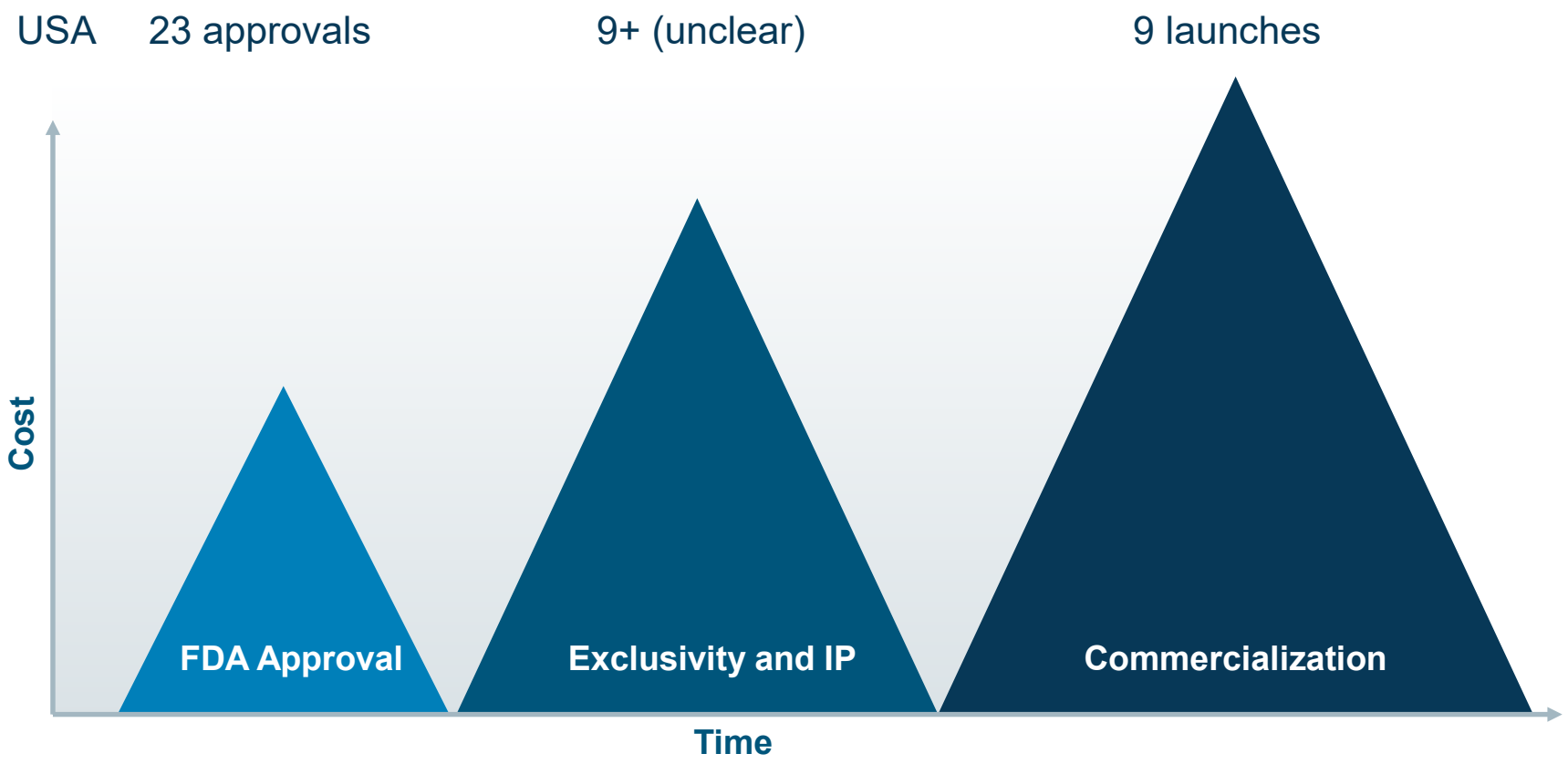

Biosimilars are being approved but not launched. SO WHAT DOES THIS HAVE TO DO WITH FDA?

Outline

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- **FDA's Biosimilar Action Plan**
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FDA's Biosimilar Action Plan (BAP)

US ADMINISTRATION HAS MADE A COMMITMENT TO BIOSIMILARS[1-3]

- Biosimilar Action Plan (BAP) published 18Jul18 concurrently with then FDA Commissioner Gottlieb's address at Brookings[4]- broad and general goals rather than specific tactics
- FDA has minimal commitments to additional guidance on biosimilars as part of their 2019 Guidance Agenda[5]
- FDA has reorganized the Office of New Drugs (OND) and elevated the role of those reviewing biosimilars
- Trump Administration's "American Patients First"[6] has many q's on biosimilars
- FDA Part 15 Hearing 4Sep18; Insulin meeting 13May19
- FDA has approved 23 biosimilars to 9 reference biologics, and has 73 products for 38 reference products being considered at FDA[7], **but sponsors are dropping programs mid-development**

FDA has the information to expedite more efficient development and more approvals already for biologics and biosimilars

1. FDA's 2018 Strategic Policy Roadmap here 11Jan18; 2. Gottlieb AHIP *Capturing the Benefits of Competition for Patients* here 7Mar18; 3. Gottlieb Statement on the Trump Administration's plan to lower drug prices here 11May18; 4. Dr. Gottelib's Brookings address here; 5. FDA 2019 Guidance Agenda here 19Jan18; 6. HHS Blueprint to Lower Drug Prices and Reduce Out-of-Pocket Costs16Jul18 here 7. SYim 25Oct19

FDA Released a Biosimilars Action Plan (BAP)[1] in July 2018 to Spur Biosimilar Competition in the US

Improve Efficiency

Standardized Tools
Standardized applications and reviews

OTBB
Develop the Office of Therapeutic Biologics and Biosimilars

Development Efficiency
Employ tools to correlate clinical response with clinical performance

Provide Clarity for Manufacturers

Ex-US Data Sharing
Facilitate use of non-US-licensed comparator products

Guidance Documents
Finalize 10 documents for development and approval of biosimilars

Purple Book
Provide more information on reference product exclusivity determinations

Develop Educational Resources

Biosimilars Website
Update website to increase understanding for providers and patients

Webinars
Host webinars about regulatory framework and development of biosimilars for health care professionals

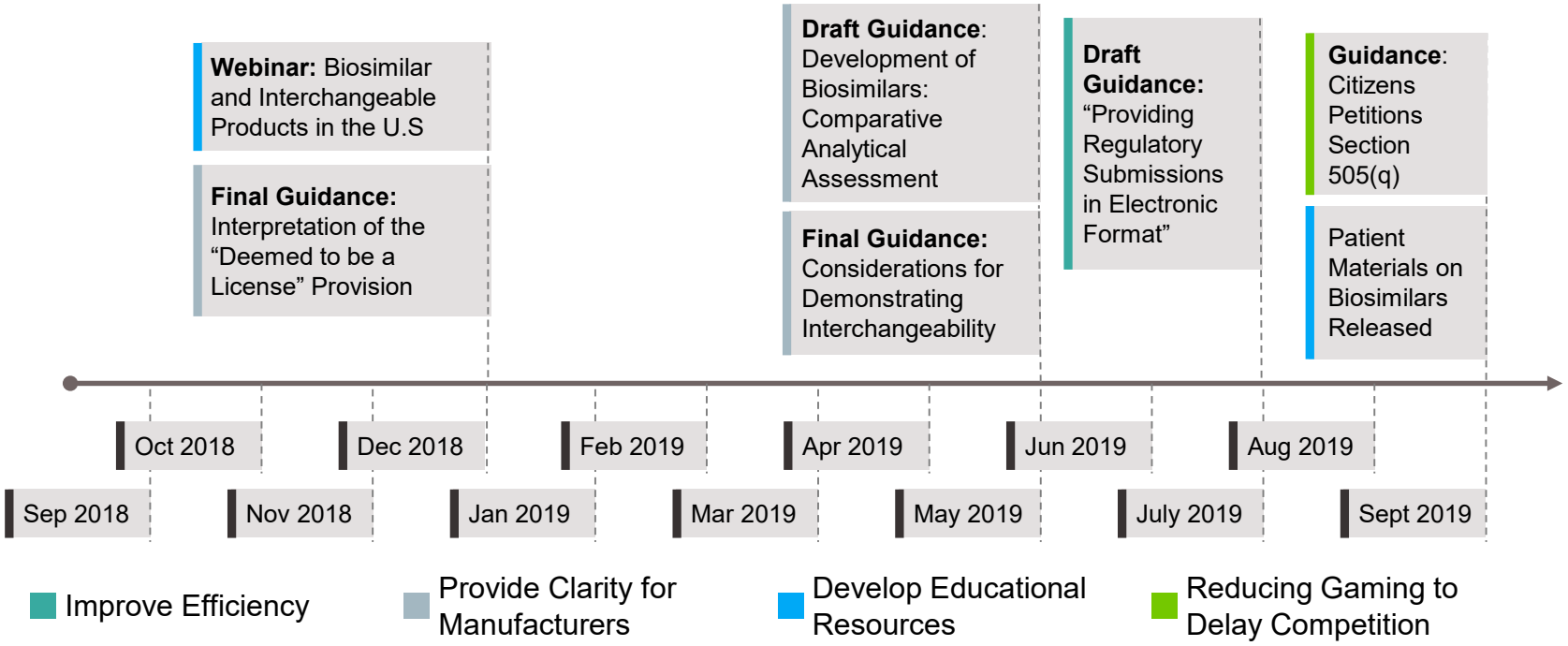
Reducing Gaming to Delay Competition

Reference Product Exclusivity
Clarify position to enforce balance between innovation and competition

Ambitious yet vague

1. FDA. "Biosimilars Action Plan: Balancing Innovation and Competition." (July 2018). https://www.fda.gov/media/114574/download

Since FDA Released BAP, It Has Followed Through on Some Aspects, Still Waiting on Others[1]



- Sarah Yim is the Acting Director of OTBB; approximately 20 other people on staff
- Purple Book has not yet been updated
- Waiting on a variety of guidance documents; FDA rescinded Statistical Approaches to Evaluate Analytical Similarity guidance[2]

OTBB: Office of Therapeutic Biologics and Biosimilars; BAP: Biosimilars Action Plan

1. Christl, Leah. "Update: Biosimilar Program in the US." Medicines for Europe Biosimilar Medicines Conference, April 27, 2018. https://www.fda.gov/media/112812/download
2. FDA. "FDA Withdraws Draft Guidance for Industry: Statistical Approaches to Evaluate Analytical Similarity." https://www.fda.gov/drugs/drug-safety-and-availability/fda-withdraws-draft-guidance-industry-statistical-approaches-evaluate-analytical-similarity

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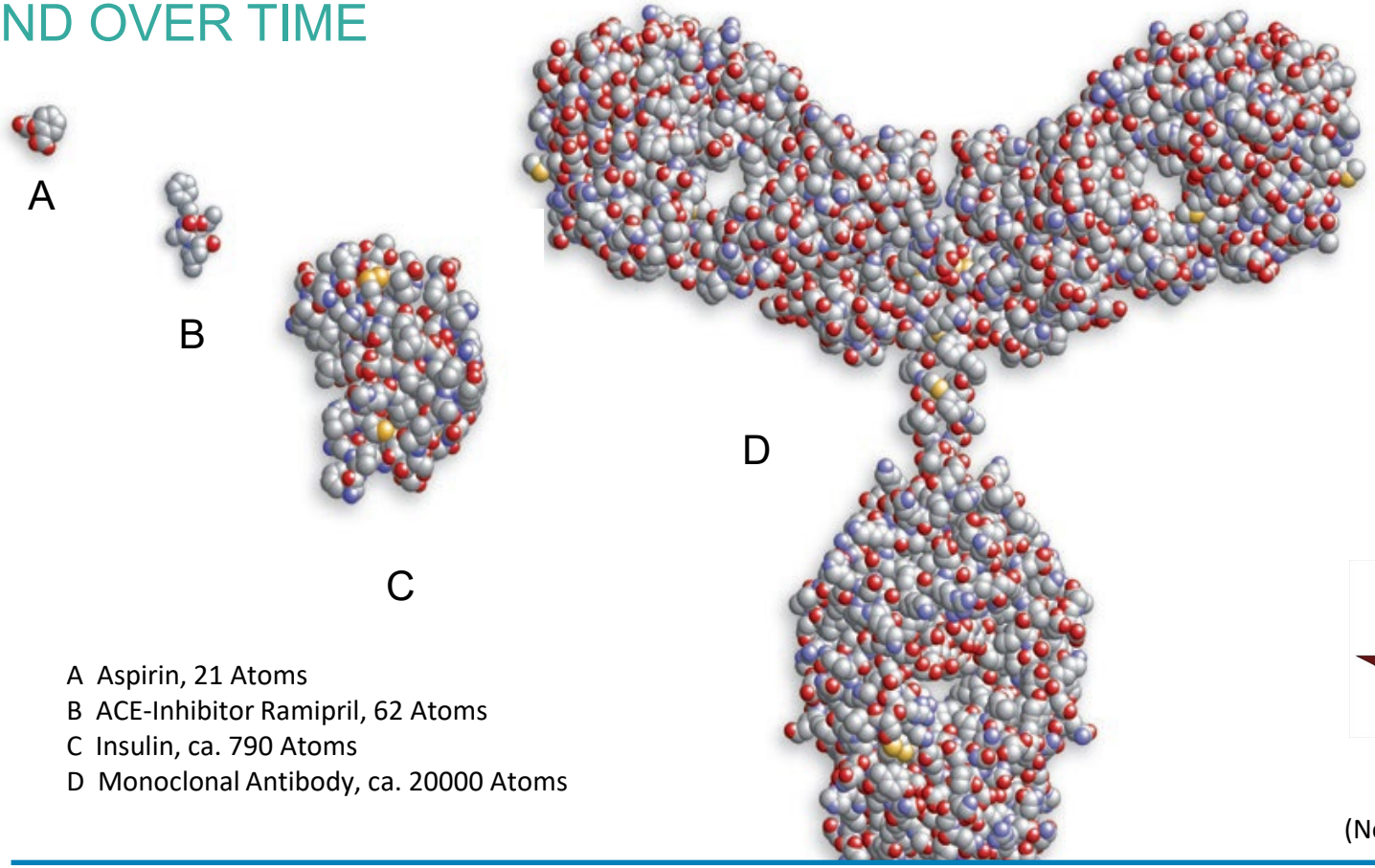
Biologics Vary in Complexity – Even Recombinant Ones

AND MANY ARE COMPLEX MIXTURES THAT VARY BATCH-TO-BATCH AND OVER TIME



A Aspirin, 21 Atoms
B ACE-Inhibitor Ramipril, 62 Atoms
C Insulin, ca. 790 Atoms
D Monoclonal Antibody, ca. 20000 Atoms

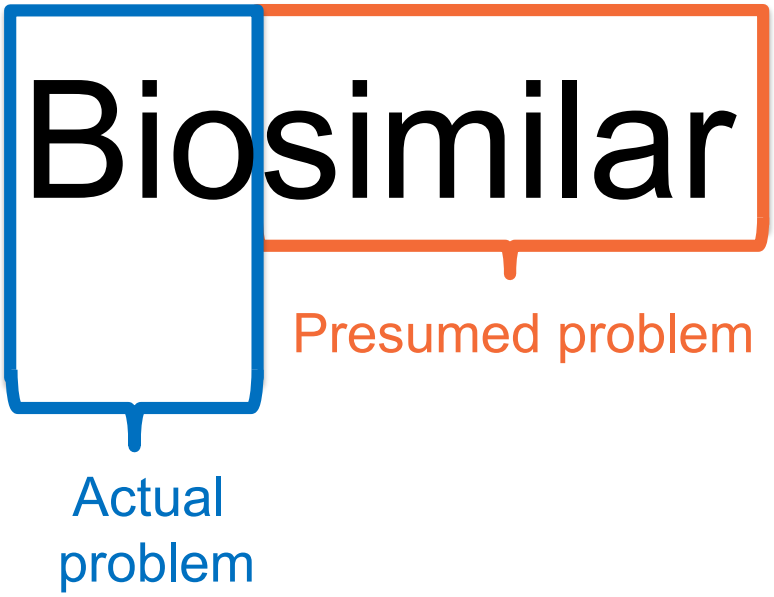
"Soup"
(Not drawn to Scale)

Once approved, complexity is no longer a relevant argument

Derived from a slide presented by Brockmeyer Biopharma GmbH
Source: VFA 2010

The Name Does Not Change the Product in the Tube

SCIENTIFIC AND REGULATORY PRINCIPLES ARE ESTABLISHED FOR ALL BIOLOGICS

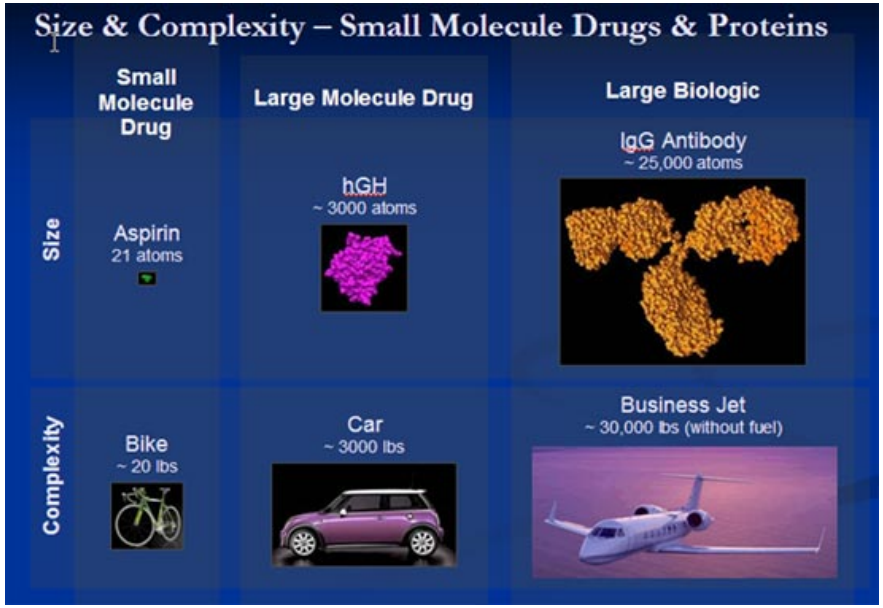


Solved by Comparability[1] in 1996, which established the "highly similar" analytical standard as a way to define a biologic

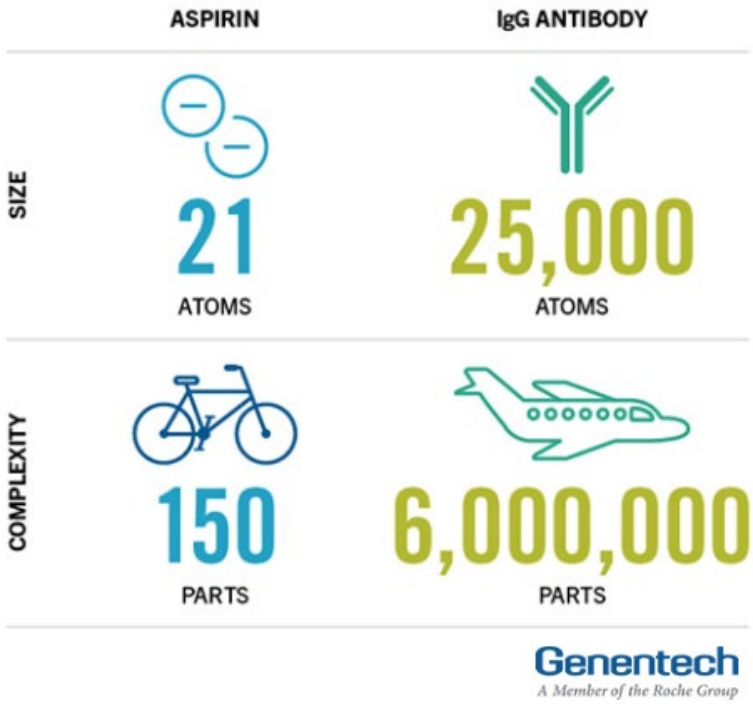
1. Demonstration of Comparability of Human Biological Products, Including Therapeutic Biotechnology-derived Products April 1996 here

Reference Standards can Complement Regulatory Decisions

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



AZBIO
ARIZONA BIOINDUSTRY ASSOCIATION



Genentech
A Member of the Roche Group

But the wheels on those bicycles, cars and planes are equally round
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

Avalere |

Manufacturing Changes are a Regulatory Norm – Subject to Review in Each Market and Each Biologic becomes "Biosimilar" to Itself

A PRODUCT THAT IS "HIGHLY SIMILAR" HAS THE "SAME" ACTIVE INGREDIENT, AND THE CLINICAL OUTCOME IS EXPECTED TO BE THE "SAME" (see ICH Q5E)

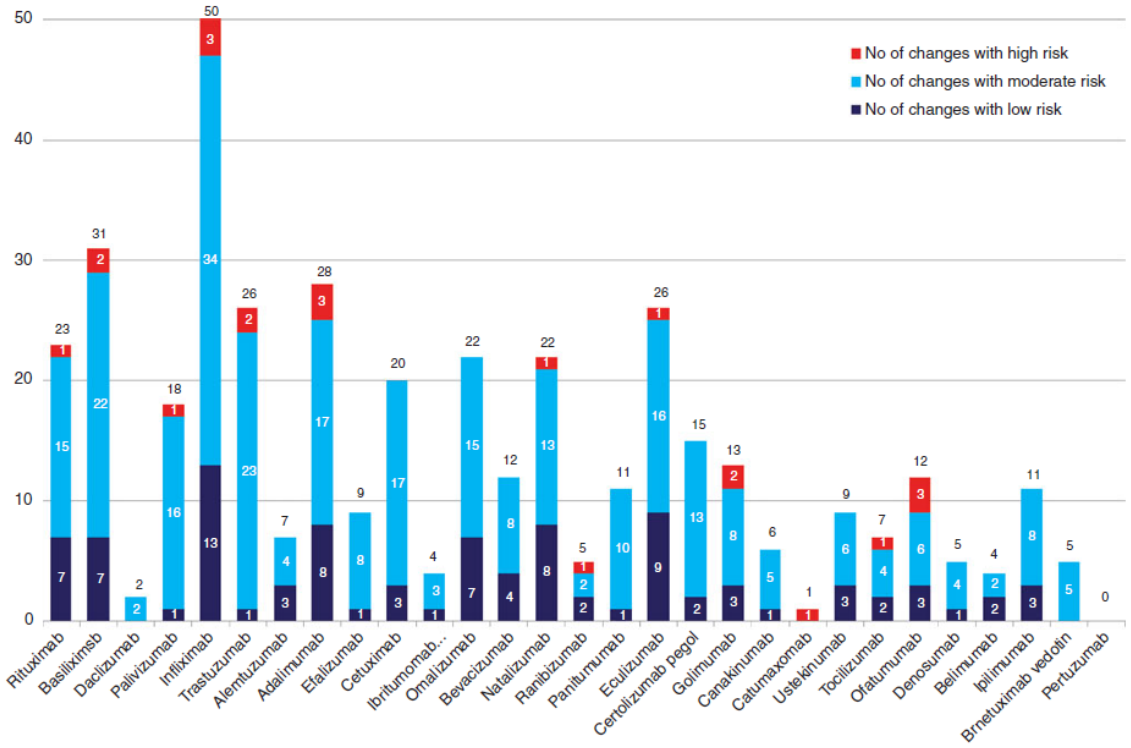


Figure 2. Number of manufacturing changes for monoclonal antibodies in their European Public Assessment Reports according to risk category (during the search period all non-proprietary names relate only to the trade named medicines listed in Table 1).

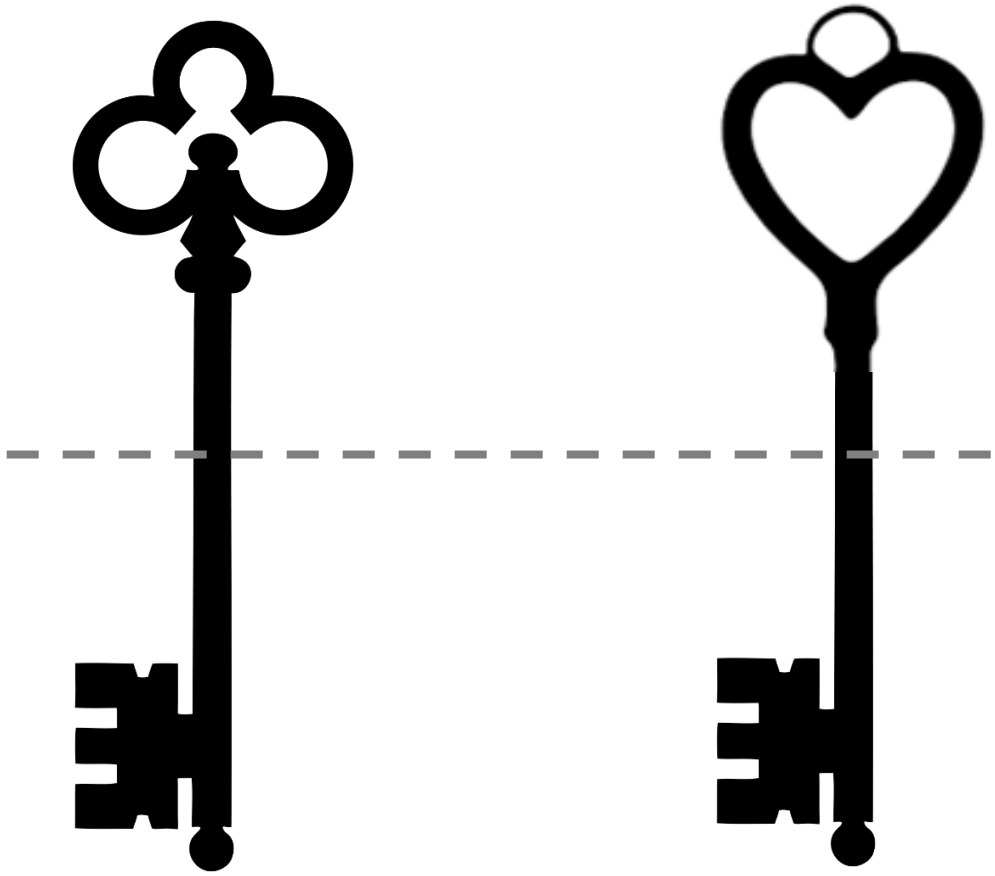
Each manufacturing change is approved by the regulators in that jurisdiction:

- Complete **extrapolation** between all indications
- **Interchangeability**
- The patient/HCP is not informed of the change because **the label on the product does not change** - the nonproprietary name stays the same when high similarity is established

THE GOOD NEWS: Extensive experience with the reference products among all stakeholders, including regulators. Only EU public

Vezér et al(2016): Authorized manufacturing changes for therapeutic monoclonal antibodies (mAbs) in European Public Assessment Report (EPAR) documents, Current Medical Research and Opinion, DOI: 10.1185/03007995.2016.1145579, available at: http://dx.doi.org/10.1185/03007995.2016.1145579

All biologics vary over time, but each functions the same clinically



Non-operative parts of the molecule may have some differences in composition and conformation

Biologically active parts of the molecule have same composition and conformation

Biosimilars apply the established principle of regulatory science that analytics predict function

Adapted from Webster CJ of BioApprovals. **Docket ID: FDA-2018-N-2689. Facilitating Competition and Innovation in the Biological Products Marketplace; Public Hearing; Request for Comments**

Development of Biosimilars Invokes Aspects of Both Originator Products and Generics

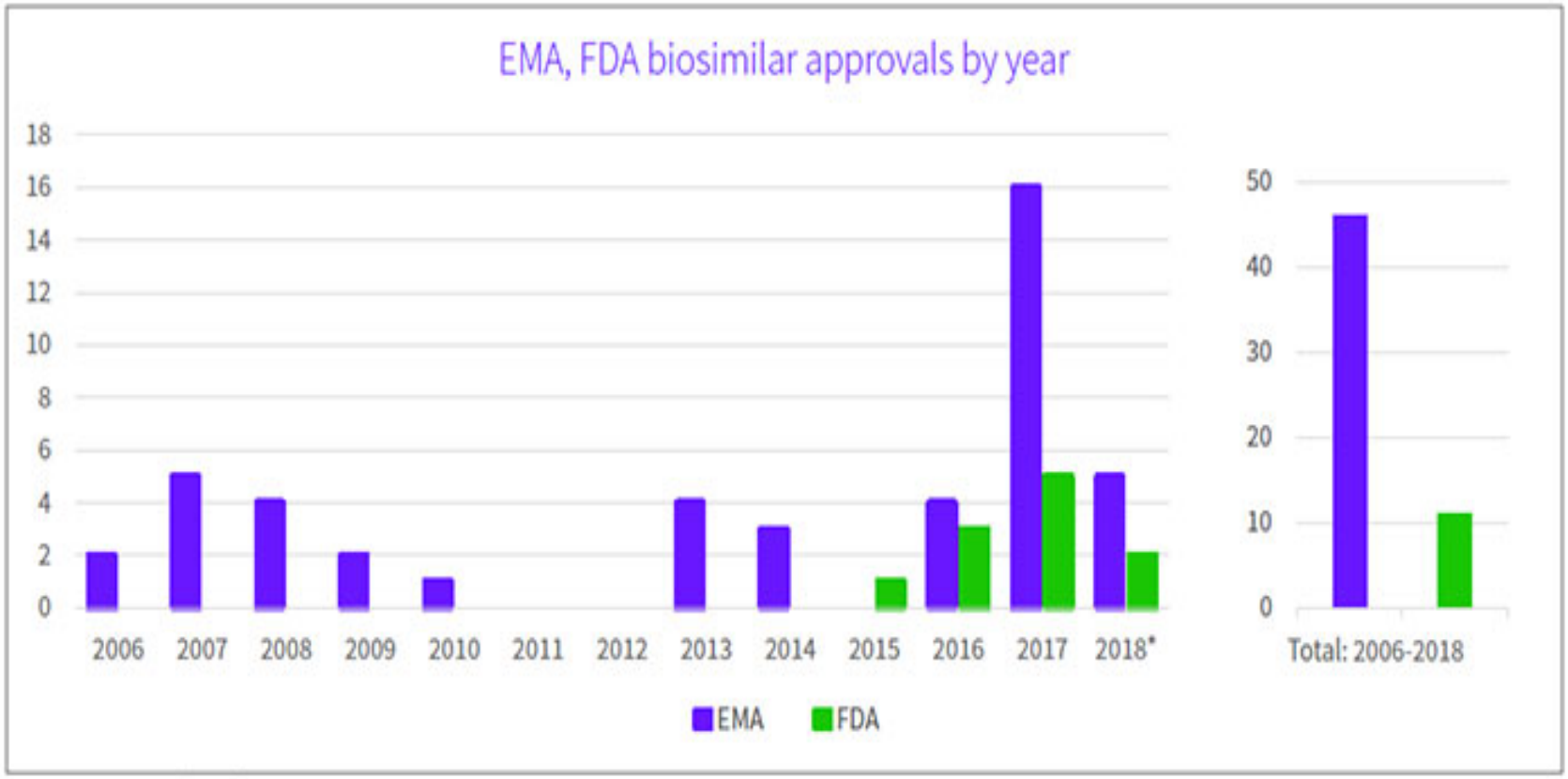
Small Molecule Generic	Biosimilar/ Interchangeable Biologic	Novel Molecular Entity
Already therapeutic options, but may be lack of access through affordability challenges		Unmet need: Lack of therapeutic options
Established MOA		Often novel mechanism of action (MOA)
Routine analytics	Exceptional Analytics	Routine analytics
Limited confirmatory clinicals (BE)	Tailored clinical studies to confirm biosimilarity	Broad clinical development program
Relies on prior finding of safety and efficacy of reference		Demonstration of de novo efficacy & safety
Clinical expertise unnecessary	Expertise in therapeutic area fundamental	
Quality Manufacturing Essential (cGMP)		

Limited companies with the necessary skill sets to achieve regulatory approval, but nothing fundamentally new required

McCamish, M., Pakulski, J., Sattler, C. and Woollett, G. (2015), Toward interchangeable biologics. Clinical Pharmacology & Therapeutics. doi: 10.1002/cpt.39, available at:: http://onlinelibrary.wiley.com/doi/10.1002/cpt.39/full

Europe and the US have different biosimilar approvals

YET US AND EUROPE ARE THE MOST HARMONIZED REGULATORILY



Source: EMA, FDA; *As of June 15

Requirements for different data sets in different regions are not scientifically or clinically justified

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)

Pharmacovigilance of Biologics in a Multisource Environment

- All medicines are subject to the same PV requirements
- US data is limited, but EU estimated 700 million patient days of treatment with biosimilars through late 2016 and no unusual or unexpected events[1]

TABLE 1 Safety Monitoring Experience with 3 Biosimilars with Total Patient Days of Treatment After Approval

EPOETIN ALFA Binocrit/Epoetin alfa Hexal/Abseamed/Novicrit	SOMATROPIN Omnitrope/Scitropin	FILGRASTIM Zarzio/Zarxio/Filgrastim Hexal
Total spontaneous (HCP, non-HCP) AEs/ADRs reported through August 31, 2016, n = 355	Total spontaneous (HCP, non-HCP) AEs/ADRs reported through September 30, 2016, n = 1,603	Total spontaneous (HCP, non-HCP) AEs/ADRs reported through September 15, 2016, n = 533
Reported as: Abseamed, n = 97 Binocrit, n = 229 Epoetin alfa Hexal, n = 18 Epoetin alpha Sandoz, n = 1 Erythropoietin Sandoz, n = 1 Novicrit, n = 1 **Unknown:** Erythropoietin alfa/epoetin alfa/erythropoietin, n = 8	**Reported as:** Omintrope, n = 1,531 Scitropin, n = 15 Somatropin BS, n = 22 **Unknown:** Somatropin, n = 35	**Reported as:** Zarzio, n = 455 Zarxio, n = 18 Filgrastim Hexal, n = 20 Filgrastim Sandoz, n = 3 Filgrastim BS, n = 1 **Unknown:** Filgrastim, n = 33 **Unknown:** G-CSF, n = 3
206,303,772 patients days through August 31, 2016 (date of PSUR: October 21, 2016)	***120,461,390 patient days*** through September 30, 2016 (date of PSUR: November 14, 2016)	***15,924,538 patient days*** through September 15, 2016 (date of PSUR: October 31, 2016)

ADR = adverse drug reaction; AE = adverse event; BS = biosimilar; G-CSF = granulocyte-colony stimulating factor; HCP = health care provider; PSUR = periodic safety update report.

No new safety concerns have been demonstrated for biosimilars.
No new monitoring mechanisms are needed because of them

1. Medicines for Europe submissions to FDA public meeting docket for Mylan's Trastuzumab Biosimilar
2. Table from J Manag Care Spec Pharm, 2017 Dec;23(12):1249-1254. https://doi.org/10.18553/jmcp.2017.23.12.1249

US Biosimilar Approvals are behind EU

SAME SCIENCE, VERY SIMILAR PEOPLE, WHAT GIVES?

The US has 23 biosimilars approved to 9 reference biologics[1], with 9 commercially available (plus 73 products for 38 reference products being considered at FDA).

Meanwhile, since 2006, Europe has gained extensive experience in a broader variety of therapeutic areas with 53 approved biosimilars approved to 15 reference medicines[2]. And as biosimilars have become available costs have gone down and patients' access increased[3]

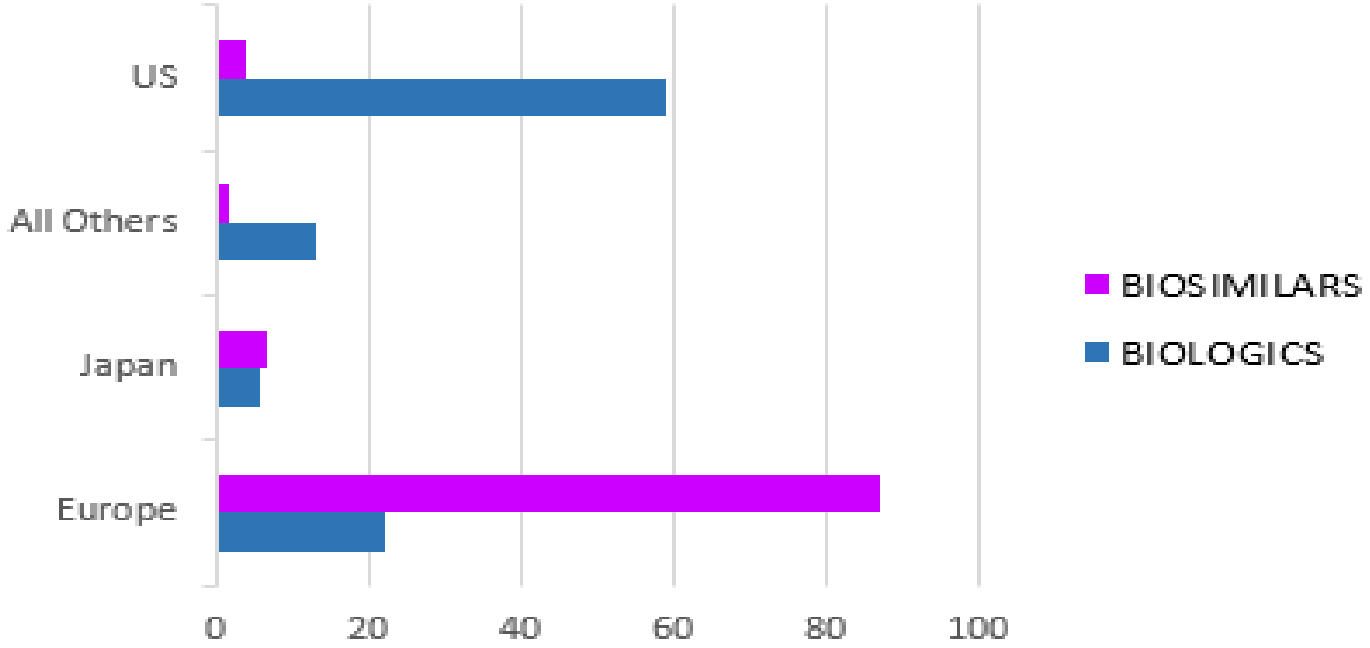
Study showed that 90% of biosimilar sales take place in EU (2016)[4]. However, given that 60% of overall biological medicines sales occur in US (2016)[4], the opportunities for biosimilars and interchangeable biologics to offer savings in the US are even greater.

The legal environment in EU and US are different, but the regulatory science on quality, safety and efficacy are the same

1. https://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm580432.htm
2. https://www.ema.europa.eu/human-regulatory/marketing-authorisation/biosimilar-medicines-marketing-authorisation
3. NHS England: Keith Ridge, Chief Pharmaceutical Officer April 2018 *Biosimilars – the National view from NHS England*
4. *IMS Health MIDAS MAT Q4 2016*

Global Sales by % Total market for Biologics & Biosimilars

WORLDWIDE BIOSIMILARS STILL FACE CONSIDERABLE CHALLENGES[1]



Biosimilar sales globally are still under 1 percent of those of originator biologics worldwide, so the room for further savings remain large and apply well beyond the U.S. and Europe.

Biosimilars comprised only 0.74% of global biologics sales in 2016, and still under 3% in 2018

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

Outline

- Context
  - FDA is simply the first challenge for US Biosimilars
  - High expectations for substantial savings through competition
  - The future of biotech depends on getting biosimilars right
- FDA's Biosimilar Action Plan
  - Recap – Biosimilars are biologics we know a lot about
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- Conclusions

Reducing Meaningless* Clinical Studies will Reduce ROI

The Current Situation in the US:

- The reference product for a biosimilar is the locally-approved 351(a) reference
- The reference product is defined by its label, not what is in the tube - unless an analytical study to bridge is conducted by each biosimilar's sponsor
- In the US, this is defined in BPCIA as

  "The term 'reference product' means the single biological product licensed under subsection (a) against which a biological product is evaluated in an application submitted under subsection (k).".

This means that even with global originator reference products we have regional biosimilars, each either creating their own analytical bridge or a complete biosimilar development programs for each jurisdiction. Such repetition is not useful and does not enhance the quality, safety and efficacy of products approved

Every biosimilar approved in every other highly regulated market will be safe and effective in America too

* *Definition* Merriam Webster = having no *meaning* especially lacking any significance

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

Enabling Global Development Will Improve Patient Access & Affordability to All Biologics

GOAL: Minimize excessive repetitive studies that provide no new data

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

If the Reference Product is the same shouldn't the biosimilar be able to be too?

BioDrugs

August 2017, Volume 31, Issue 4, pp 279–286 | Cite as

A 'Global Reference' Comparator for Biosimilar Development

Authors | Authors and affiliations

Christopher J. Webster, Gillian R. Woollett

Open Access | Current Opinion

First Online: 19 May 2017

9 Shares | 3.3k Downloads | 9 Citations

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Either one believes in the clinical relevance of the analytical match or one doesn't

… And a bridge for one confirms a bridge for all

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

A Proposal to Expedite Biosimilar Development Worldwide[1]

A 'GLOBAL REFERENCE' COMPARATOR FOR BIOSIMILAR DEVELOPMENT

Based upon the shared development history **a single reference version of the originator biologic may be selected for global biosimilar development** if the following criteria are met:

- The chosen reference has been approved in an ICH compliant jurisdiction (assures comparability);
- The formulation of the chosen reference has the same pharmaceutical form, route of administration, content of active pharmaceutical ingredient (API);
- There is substantial evidence in the public domain that the chosen reference and the local reference product have been approved in their respective jurisdictions on the basis of essentially the same original data.
- WHO is looking to PreQualify Biologics (already do for vaccines)

Supports harmonization of regulations and adoption of same science worldwide – both enhance trust in regulators and biopharma, and are pro-competition

1 Christopher J. Webster, Gillian R. Woollett (2017) ***A 'Global Reference' Comparator for Biosimilar Development*** BioDrugs here

Immediate Opportunity for Even More Efficient Biosimilar Development

Open Access:
https://link.springer.com/article/10.1007%2Fs40259-019-00371-4

Unnecessary clinical studies lack scientific validity and are necessarily unethical. They are simply barriers to competition

Christopher J. Webster, Anny C. Wong, Gillian R. Woollett (2019) **An Efficient Development Paradigm for Biosimilars**, BioDrugs
https://link.springer.com/article/10.1007%2Fs40259-019-00371-4

Harmonized regulatory approaches help access worldwide

ESTABLISHED REGULATORY SCIENCE WORKS

- Europe has led on biosimilars - the ROW has successfully applied the same approaches, and they became WHO's 2009 Guidelines
- Post approval experience is pooled through increasingly harmonized monitoring systems and is showing biosimilars behave just like their reference products in clinical practice
- For investments in biosimilars to maximize access and affordability for patients, including in the US, repetitious studies need to be avoided, especially clinical trials – PK is enough for most biosimilars
- Other initiatives, such as Real World Data/Evidence (RWD/E), will contribute to global data sets and international confidence

US barriers to biosimilars may create barrier to global access that ultimately compromises the health of 7 billion people including our own

Christopher J. Webster, Anny C. Wong, Gillian R. Woollett (2019) **An Efficient Development Paradigm for Biosimilars**, BioDrugs
https://link.springer.com/article/10.1007%2Fs40259-019-00371-4

Countries are Learning and Sharing

Same Science, Same Data, Same Regulatory Decisions Worldwide?

Progress is being made:

- **WHO Prequalification of Biologics**, plus ICMRA - 29 regulatory authorities from around the world, plus WHO, have expressed confidence in biosimilars[1]
- **ICH** and **Compendia, such as USP**, cover a lot of the shared quality expectations for all biologics
- Reciprocal recognition of **facility inspections** US and EU1
- **FDA Project Orbis** – applies to US, Canada and Australia for **new cancer therapies**[1]
- Broader effort instigated by Australia's TGA to create a network of ***Comparable Overseas Regulators (CORs)*** – Canada, Singapore, Switzerland, EU, UK, US[2]. These sister regulators are now part of a process for speeding up drug approvals by using assessment reports from comparable drug regulators.

Massive opportunity that applies to all biologics; never just biosimilars

1. ICMRA Statement here; 2. Mutual Recognition promises new framework for pharmaceutical inspections for US & EU, 2017 here; 3. Avalere *Insight on FDA's Project Orbis* here; 4. Pink *Australia To Use Japanese Reports For Faster Drug Approvals* 28Oct19 here

Regulatory Science for Biologics is Established and Works

OPPORTUNITIES FOR MORE EFFICIENT DEVELOPMENT

The set of scientific peer-reviewed papers that would change the regulatory environment for biosim's worldwide were they to be implemented are:

1. *Interchangeability of Biosimilars: A European Perspective* Jan 2017[1]
2. *A 'Global Reference' Comparator for Biosimilar Development*. May 2017[2]
3. *An Efficient Development Paradigm for Biosimilars* Aug 2019[3]
4. *Insulins as Drugs or Biologics in the USA: What Difference Does it Make and Why Does it Matter?* Aug2019[4]
5. *Evolution of the EU Biosimilar Framework: Past and Future* Sep 2019[5]
6. *Delivering on the Promise of Biosimilars* Oct 2019[6] new

Implementation of state-of-the-art regulatory science is key to optimal biosimilar development, and for updating originator biologics development globally

1.here; 2. here; 3. here; 4. here; 5. here; 6. here

Outline

- Context
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  - High expectations for substantial savings through competition
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  - Recap – Biosimilars are biologics we know a lot about
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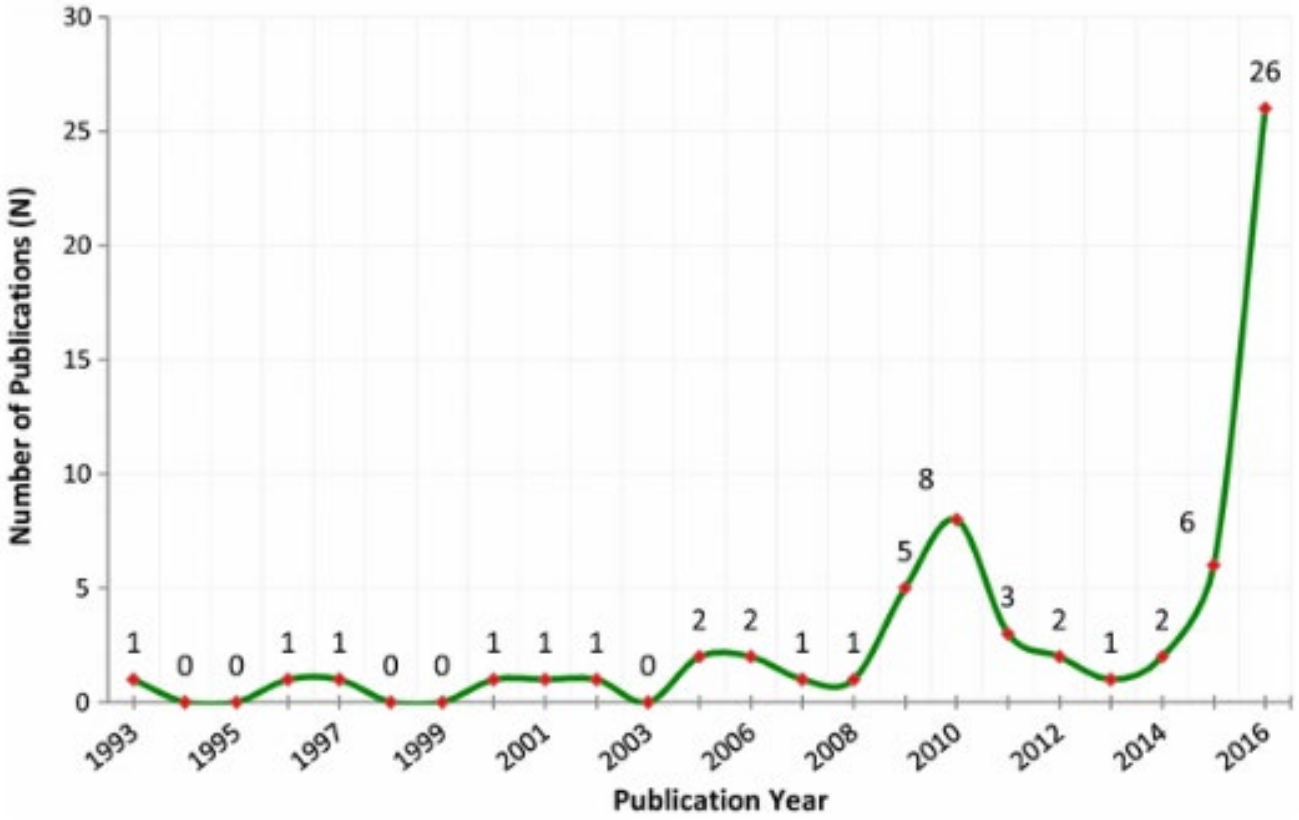
Biosimilars have increased the interest in switching

SWITCHING BETWEEN BIOLOGICS IS COMMON,AND COMPARABILITY THE NORM



Likely an economic basis for this interest, but no regulatory science one

Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes
https://link.springer.com/article/10.1007/s40265-018-0881-y

Interchangeability – Unique to US Law

Dr. Leah Christl for 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.**

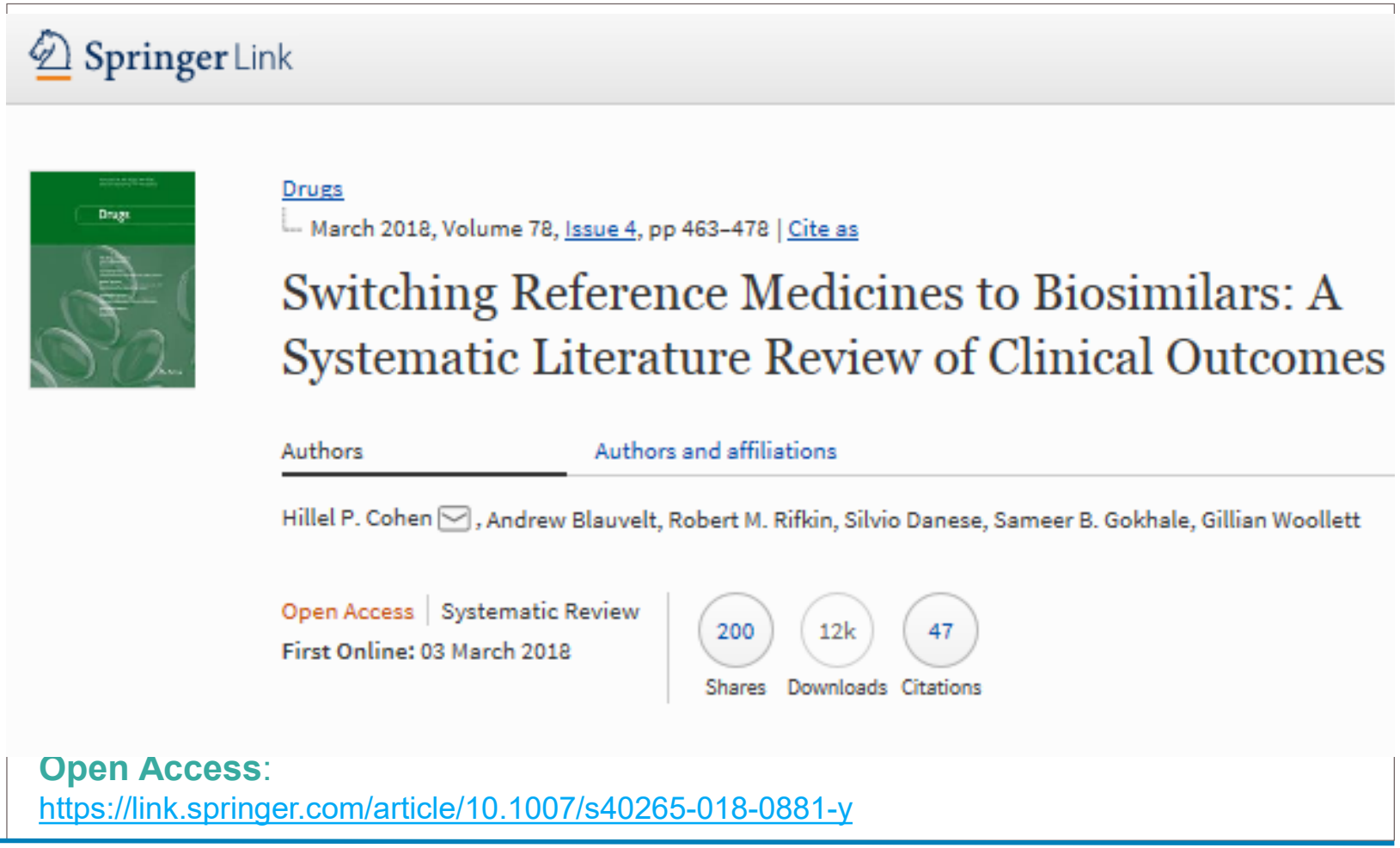
However, she then explained in some detail that interchangeability in the US is a designation **solely for the purposes of substitution by other than the prescriber**. And for such pharmacist substitution the law was clear that an additional designation from FDA was available.

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. Regulatory consistency matters.
Switching is not a legitimate scientific or clinical concern

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

Data shows switching is not a concern



Springer Link

Drugs

March 2018, Volume 78, Issue 4, pp 463–478 | Cite as

Switching Reference Medicines to Biosimilars: A Systematic Literature Review of Clinical Outcomes

Authors | Authors and affiliations

Hillel P. Cohen, Andrew Blauvelt, Robert M. Rifkin, Silvio Danese, Sameer B. Gokhale, Gillian Woollett

Open Access | Systematic Review

First Online: 03 March 2018

200 Shares | 12k Downloads | 47 Citations

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https://link.springer.com/article/10.1007/s40265-018-0881-y

Switching from the reference to the biosimilar raises no safety or efficacy concerns (14,255 unique patients)

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Christopher J. Webster, Gillian R. Woollett (2018) Comment http://link.springer.com/article/10.1007/s40259-018-0297-y on "The End of Phase 3 Clinical Trials in Biosimilars Development?" by Xavier Frapaise https://doi.org/10.1007/s40259-018-0287-0

What do we do when the US is not First?

CATCH UP, THROUGH LEAP FROGGING, USE THE EXPERIENCE OF OTHERS

- Most biosimilars have followed the European approach –
  - law was available first (2004 revisions to pharmaceutical laws)
  - IP less problematic (shorter exclusivity, fewer patents expiring sooner)
  - reference product available
  - standard of quality, safety and efficacy are the same as ours
  - Acceptable world wide - WHO has largely adopted EU guidelines
- Usually the US is a secondary market for biosimilars, but also the biggest and most profitable for originator biologics
  - US is a priority market (60% of global market by $)
  - Drug prices a big issue, biosimilars offer a competitive solution
  - Resistance highest here, but more data available to users by time of launch

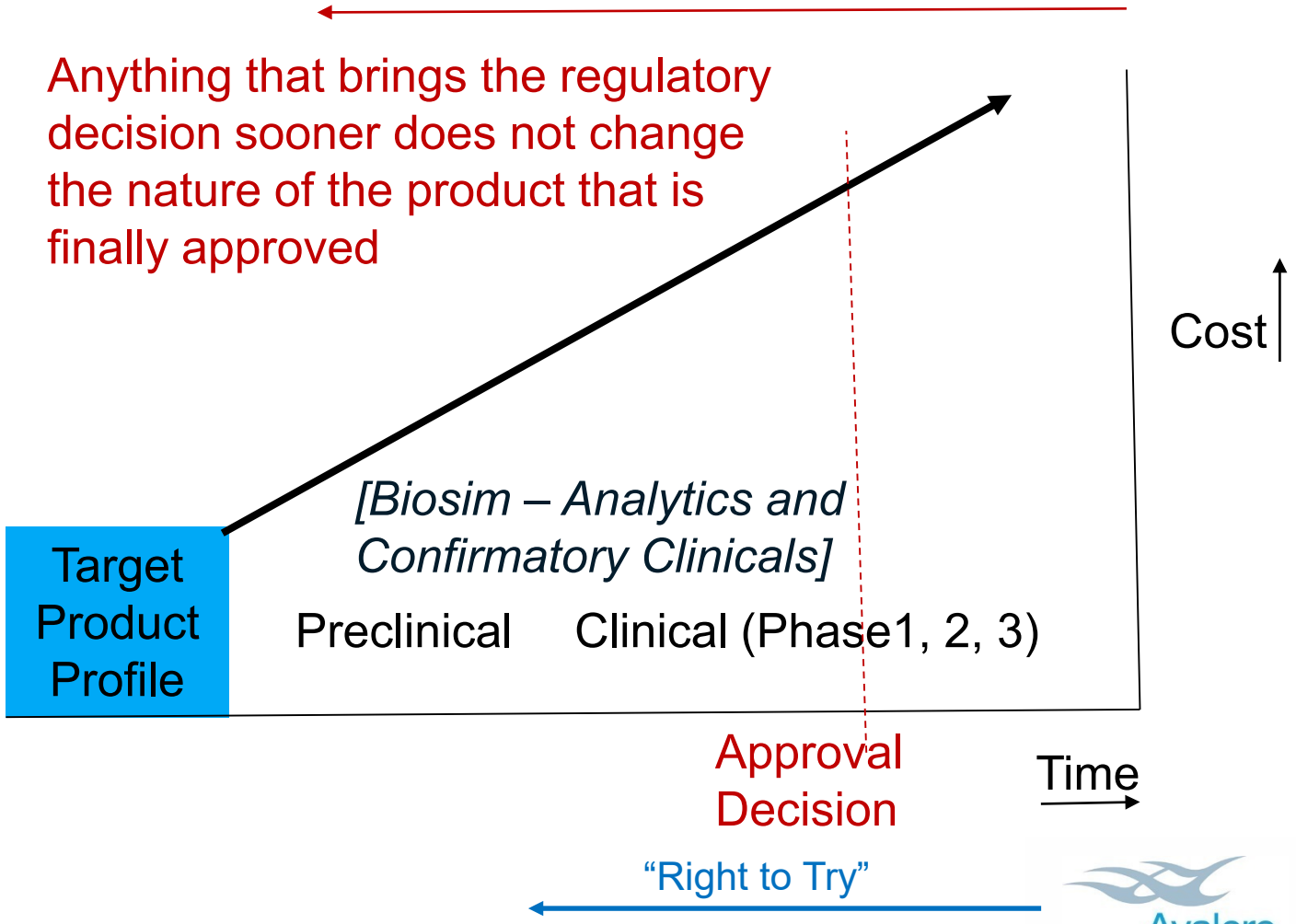
Seize opportunity to capture EU experience & optimize efficiency of biosimilar approval in US to support access worldwide

Outline

- Context for all biologics
  - It is always about the Economics
  - Terminology Reminders
  - Global Context – Plus a Bit of History
- Current Landscape – So where are we in the US with biosimilars?
  - The Reference Product Matters – simply solved
  - Switching Frees the Market, but does Interchangeability matter?
- **Conclusions**

Build Medicines that are “fit for purpose”

ACHIEVING ACCESS & AFFORDABILITY IS KEY FOR ALL BIOLOGICS



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Increasing Concurrent Market Entry Through Harmonization

TIMING OF PRODUCT APPROVAL AND LAUNCH ALWAYS MATTERS

GLOBAL

ACCESS
Patients are everywhere

SCIENCE
Essentially global

Companies DEVELOP AND MANUFACTURE for more than one market[1]

NAMING
Historically have had global norms[2]

REGIONAL/NATIONAL

Regulations are regional with some harmonization for drugs, and innovator biologics

IP varies, and getting a little better harmonized, but barely

Healthcare systems vary
Determines commercialization
(ROI, 1y & 2y markets)

PATIENT ACCESS REQUIRES APPROVAL, LAUNCH & COMPETITION BASED ON VALUE

1. WHO Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) See: http://www.who.int/biologicals/en/
2. WHO Administers the International Nonproprietary Naming conventions, see: http://www.who.int/medicines/services/inn/en/

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], IPRF[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, especially to biosimilars
- 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 biologics), and regulatory hurdles (e.g. Inspections)

Trust in regulatory authorities and the basis of their decisions is critical and must be consistent to be credible

1. International Committee for Harmonization http://www.ich.org/home.htm
2. International Pharmaceutical Regulators Forum https://www.i-p-r-f.org/index.php/en/iprf-network/mandate/l

Reduction in Post-Market Commitments

ALL CLINICAL STUDIES ARE A TAX ON PATIENTS AND MUST ADD VALUE

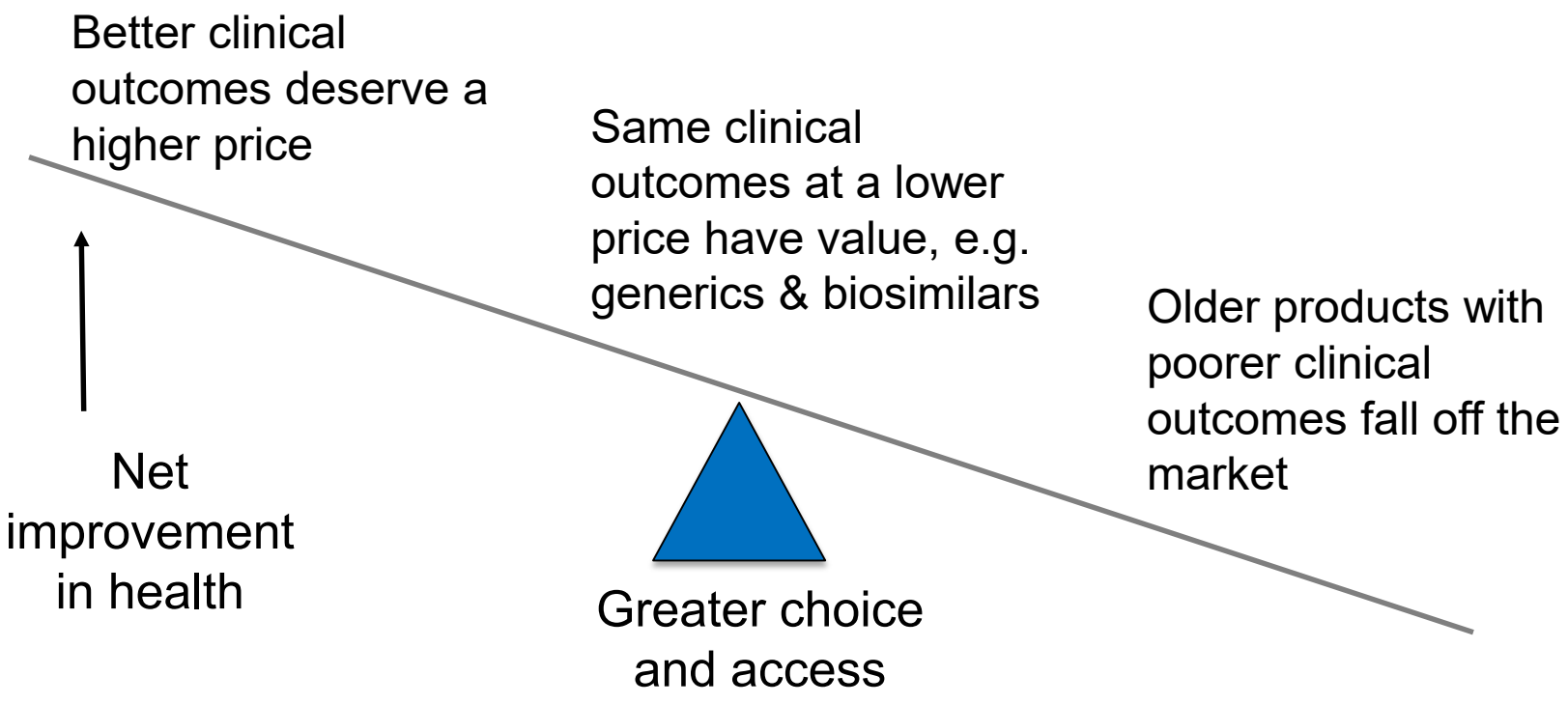
- Clinical studies that are unnecessary are ALWAYS unethical
- Meaningful data is way more than reassuring data, or nice to know – it is essential data

- Harmonization of pharmacovigilance will allow better bigger data set 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)

Coordinated studies that provide data for approval in multiple jurisdictions concurrently creates predictability

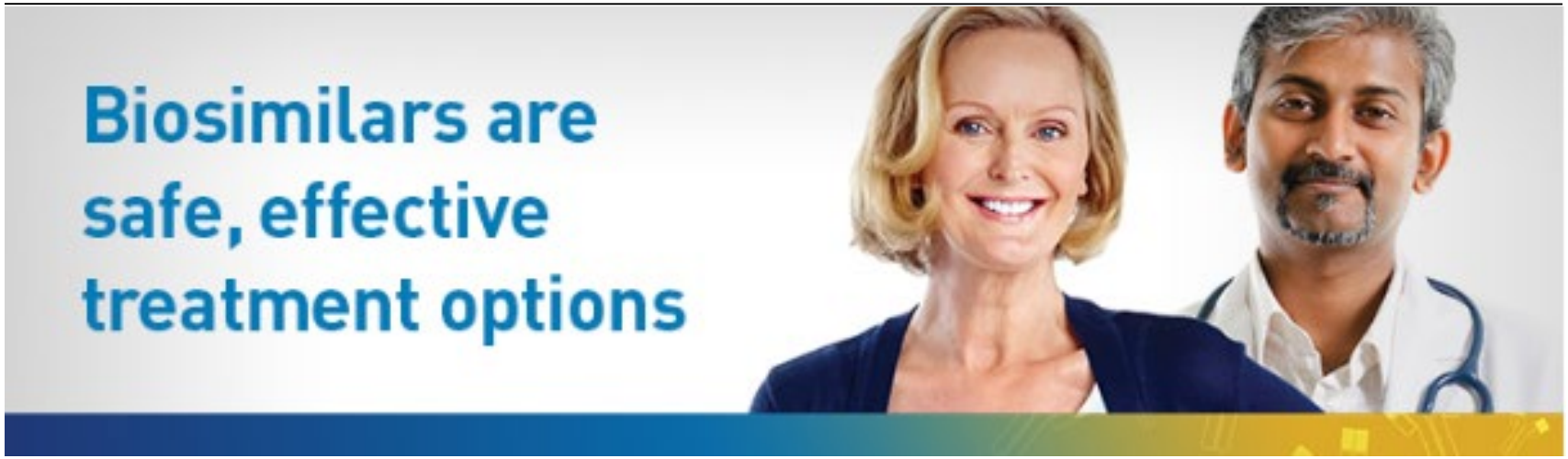
Payer/ Provider Recognition of Value

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

FDA has taken steps, but needs to run not walk



- FDA Biosimilars Home Page (here)
- Information on US approved biosimilars (here)
- Guidance for industry (here)
- Patient and Prescriber Outreach Materials (here)
- Biosimilar Action Plan – Balancing Innovation and Competition (BAP) (here)

FDA can do more to explain that all biologics vary and that is OK – quality, safety and efficacy for all biologics is still ensured

https://www.fda.gov/drugs/therapeutic-biologics-applications-bla/biosimilars

A Second Reformation: Returning Biosimilar Regulations To Scientific Roots[1]

BIOSIMILAR DEVELOPMENT

- If the reference used the same clinical studies, it is the same product globally
- A PK match is the most sensitive clinical study - enough for biosimilar approval

The science is asked and answered – the challenge now is consistency in its implementation regulatorily, independent of business model

1 https://www.biosimilardevelopment.com/doc/a-second-reformation-returning-biosimilar-regulations-to-scientific-roots-0001

Biosimilar means similar and not the same

Human clones are not inherently bad…

For ALL medicines it is always a matter of trust…

And I would take her kidney or bone marrow or blood any time as fully interchangeable AND substitutable…

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We Look Forward to Your Questions

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