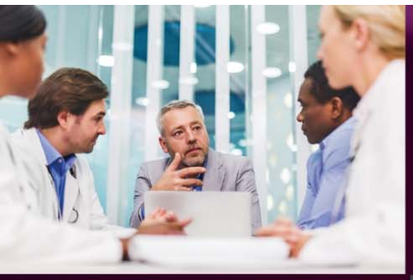

Biosimilars in Practice:

A Guide for Managed Care Professionals

Jointly provided by

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Professional Excellence in Medical Education

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Held in conjunction with

AMCP 2018 NEXUS
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Differentiating Biosimilars and Reference Products: Developmental and Regulatory Pathways

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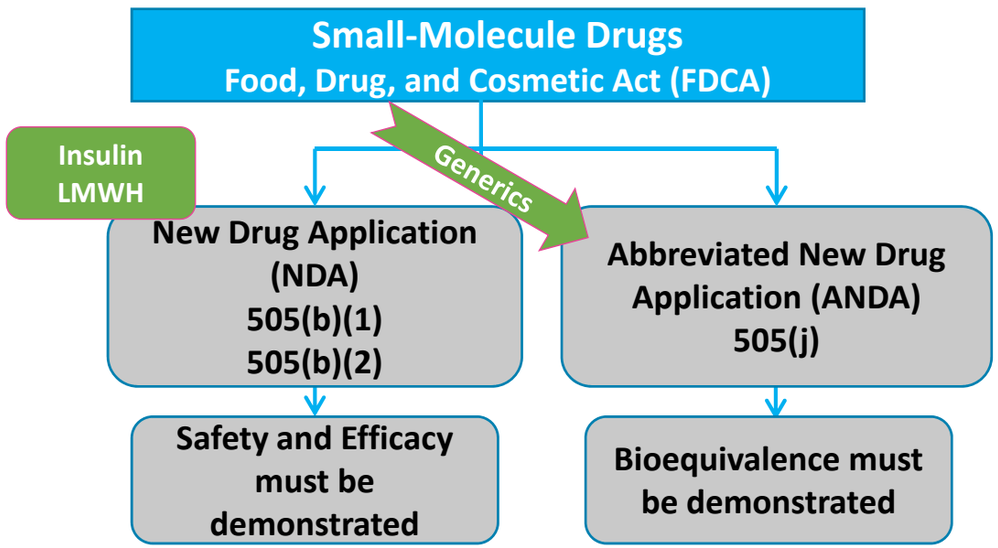
Regulatory Pathway for Biosimilars

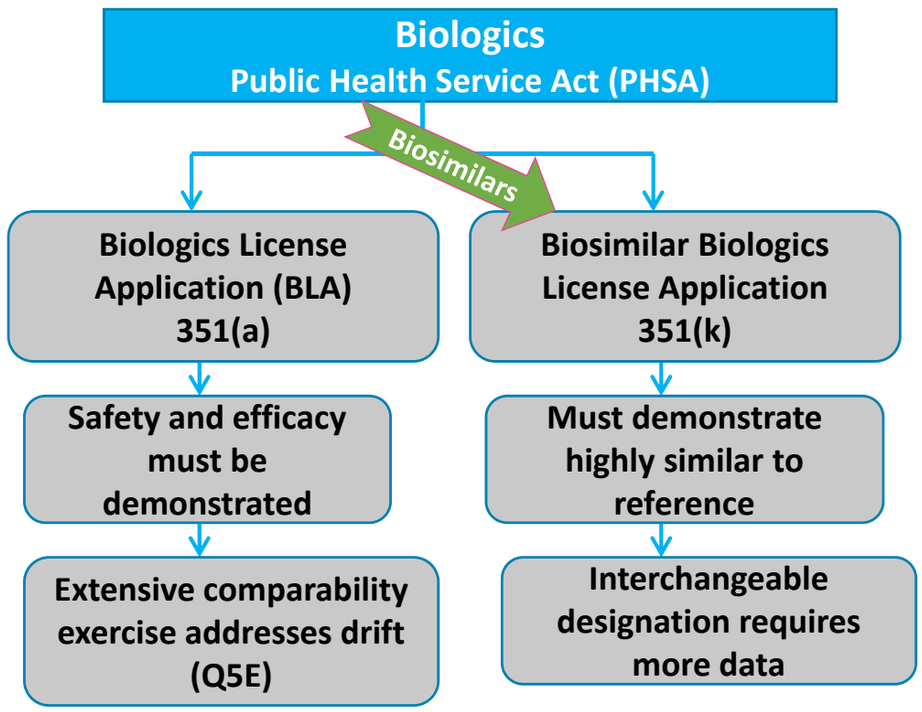
Biologics Price Competition & Innovation Act – BPCI Act of 2009: Passed March 23, 2010

- A biologic product submitted in a 351(k) application that has been shown to be highly similar to the reference product …notwithstanding minor differences in clinically inactive components
  - for which there are … no clinically meaningful differences … in terms of the safety, purity, and potency of the product …
  - … must utilize same MOA for the conditions of use prescribed
  - … same route of administration, dosage form, strength … and proposed conditions of use as reference product
  - … expected to produce same clinical result in any given patient…"

FDA.gov. Biologics Price Competition and Innovation Act of 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf. Updated March 23, 2010. Accessed September 2018.

Approval Pathways in the US





Biologics Price Competition and Innovation Act approved as part of the Accountable Care Act in 2010 authorized the FDA to create an abbreviated pathway for biosimilars approval

New Drug Application. FDA website. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/default.htm. Updated March 29, 2016. Accessed September 2018.
Abbreviated New Drug Application. FDA website. http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics. Updated May 17, 2018. Accessed September 2018.
Biologics License Applications Process. FDA website. http://www.fda.gov/BiologicsBloodVaccines/DevelopmentApprovalProcess/BiologicsLicenseApplicationsBLAProcess/default.htm. Updated February 2, 2018. Accessed September 2018.
Biosimilars. FDA website. https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/Biosimilars/default.htm. Updated September 6, 2018. Accessed September 2018.

Approved Biosimilars: US vs. EU

United States			European Union		
Reference Biologic	*# of Biosimilars*	*# Marketed*	*Reference Biologic*	*# of Biosimilars*	*# Withdrawn**
Adalimumab	2		Adalimumab	4	
Etanercept	1		Etanercept	2	
Pegfilgrastim	1	1	Pegfilgrastim	2	
Infliximab	3	2	Infliximab	4	
Bevacizumab	1		Bevacizumab	1	
Filgrastim	2	2	Filgrastim	9	2
Trastuzumab	1		Trastuzumab	2	
Erythropoietin	1		Erythropoietin	5	
			Follitropin	2	
			Rituximab	6	
			Enoxaparin	2	
			Teriparatide	2	
			Somatropin	2	1

*None of the biosimilars withdrawals in the EU were due to efficacy or safety concerns

Biosimilars Approved in the US. Generics and Biosimilars Initiative website. http://www.gabionline.net/Biosimilars/General/Biosimilars-approved-in-the-US. Updated August 31, 2018. Accessed September 2018.

Characterization of Biologics/Biosimilars

- EMA: Comparable: Quality, Safety, and Efficacy

- US FDA: Highly similar or interchangeable; no clinically meaningful differences in terms of Safety, Purity and Potency
  - Entirely independent, complete CMC* section
  - Biosimilar will have more analytical data than innovator product
    - Reverse engineering
    - Extensive comparative data on innovator and biosimilar

*CMC= chemistry, manufacturing, and controls

Kozlowski S, Woodcock J, Midthun K, Sherman RB. *N Engl J Med*. 2011;365(5):385-8.

FDA Biosimilar Guidance Documents: 2012–2019

2012

- *Quality Considerations (draft)*
- *Scientific Considerations (draft)*
- *Questions and Answers (draft)*

2014

- *Clinical Pharmacology (draft)*
- *Reference Product Exclusivity (draft)*

2015

- *Quality Considerations*
- *Scientific Considerations*
- *Questions and Answers*
- *Additional Questions and Answers (draft)*

2016

- *Labeling (draft)*

2017

- *Nonproprietary Naming*
- *Interchangeability*

2019

- *Labeling*

1. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. FDA website. https://www.fda.gov/ucm/groups/fdagov-public/documents/document/ucm291128.pdf. Published April 2015. Accessed April 2017.
2. Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product. FDA website. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm291134.pdf. Published April 2015.Accessed April 2017.
3. Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm444661.pdf. Published April 2015. Accessed April 2017.

Biosimilar Guidance: Determination of Interchangeability

- Determination of Biosimilar Interchangeability: 1/2017
  - "An interchangeable product may be substituted for reference product without intervention of the health care provider who prescribed the product"
  - Sample size of switching study should be based on PK considerations
  - The switching arm expected to incorporate ≥2 separate exposure periods to each of 2 products (ie, ≥ 3 switches with each switch crossing over to the alternate product)
  - Last switching interval should be from US-produced reference product to proposed interchangeable product, duration of exposure after last switch to allow for washout of reference product (ie, ≥3 T ½)

Considerations in Demonstrating Interchangeability With a Reference Product. FDA website. www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm537135.pdf. Published January 12, 2017. Accessed April 2017.

Biosimilar Interchangeability

- No FDA guidance until draft published in Jan 2017; thus, initial biosimilars approved are not “interchangeable”
- Guidance also uses a **“totality of the evidence” approach**
- Expected to produce the same clinical result as the reference product **in any given patient**
- **“The risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such an alternation or switch”**

Considerations in Demonstrating Interchangeability with a Reference Product. FDA website. https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm537135.pdf. Published January 12, 2017. Accessed September 2018.

Biosimilar Guidance: Nonproprietary Naming

- **Nonproprietary Naming, Final: 1/2017:** nonproprietary or proper name with designated random 4-letter suffix to facilitate pharmacovigilance
    - Companies submit 10 randomly generated suffixes to FDA for consideration as part of the naming of biologics
- FIP and others have recommended the use of INNs with small molecule medicines to facilitate therapeutic interchange and substitution
- Pharmacovigilance needs have resulted in WHO and regulatory bodies to encourage the use of an **INN plus a biologic qualifier** for all biologic products
    - "Non-meaningful suffix"
- Concern regarding potential for errors when communicating using four-letter suffix that is not memorable ("devoid of meaning")

Biological Qualifier: an INN Proposal: Programme on International Nonproprietary Names. World Health Organization website http://www.who.int/medicines/services/inn/WHO_INN_BQ_proposal_2015.pdf. Published October 2015. Accessed September 2018.
Nonproprietary Naming of Biological Products. FDA website. https://www.fda.gov/downloads/drugs/guidances/ucm459987.pdf. Published January 2017. Accessed October 14, 2017.
Stevenson JG, Green L. Biologics, Pharmacovigilance, and Patient Safety: It's All in the Name. *J Manag Care Spec Pharm*. 2016;22(8):927-30.

Scenario with the Listing of Multiple Biologics in Electronic Systems

Filgrastim-rbsz	
Filgrastim-sndz	
Filgrastim-trby	
Filgrastim-zsrc	

VS.

Filgrastim-rbsz	Ratiograstim*
Filgrastim-sndz	Zarxio
Filgrastim-trby	Stimogram
Filgrastim-zsrc	Neupogen

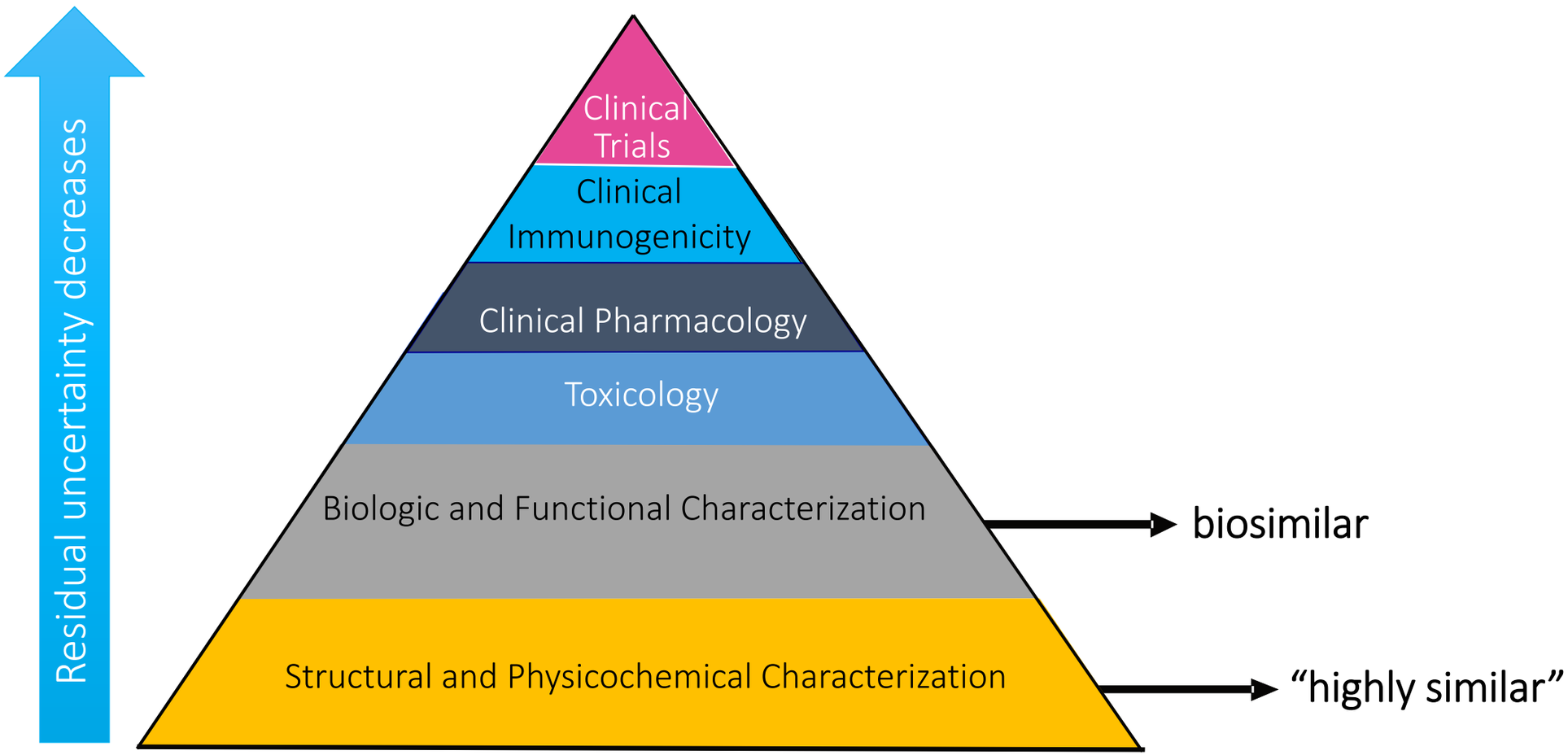
Which scenario do you believe is less prone to wrong-selection errors by prescribers, pharmacists, technicians, nurses?

* Brand names in this column hypothetical or based on EU names not linked to specific INN+suffix

INN = International Non-proprietary Name

Biosimilars versus Reference Biologics

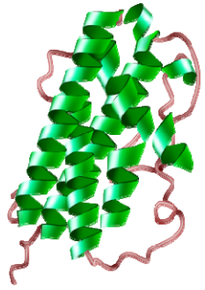
Biosimilars Must be Systematically Engineered to Match Reference Product



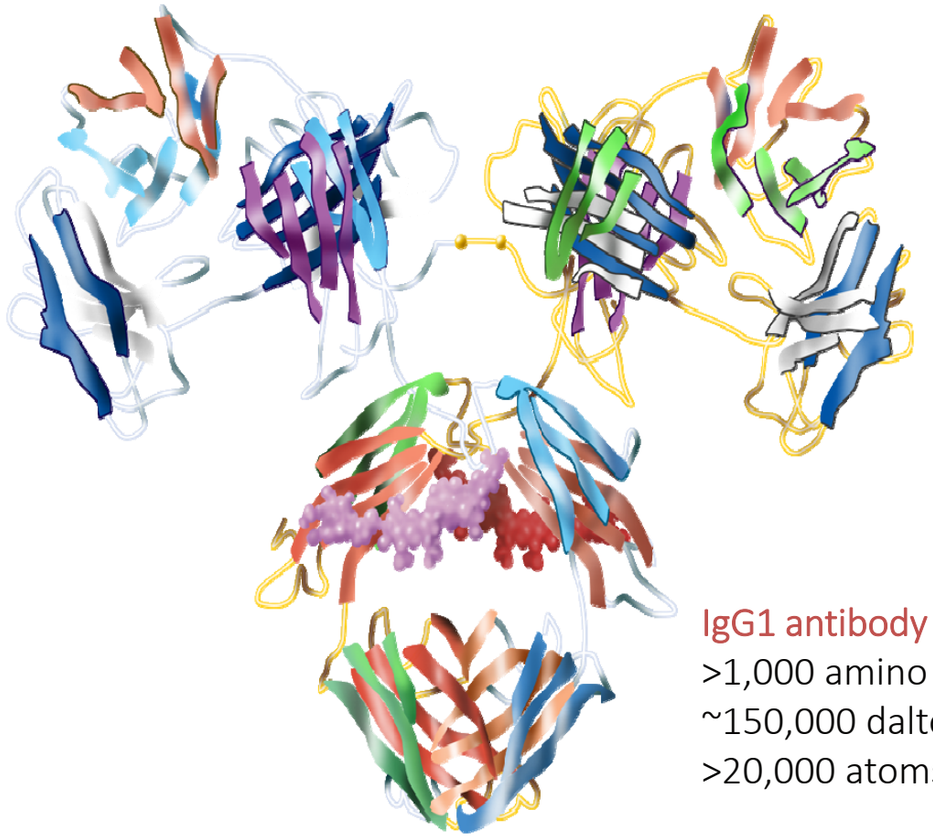
The Challenge with Biosimilars Is Knowing which Differences Matter Clinically

Aspirin
~180 daltons
21 atoms

Insulin
51 amino acids
~5,800 daltons
788 atoms



Somatropin
191 amino acids
~22,000 daltons
3,091 atoms



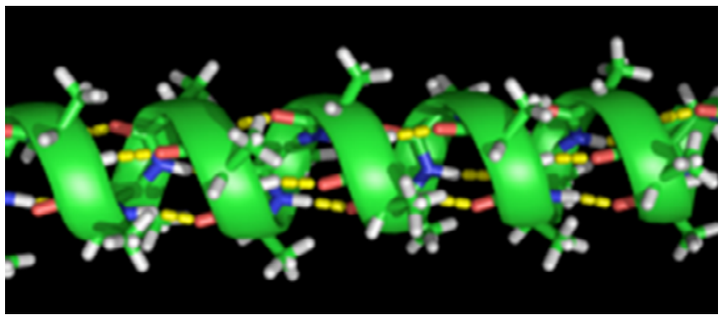
IgG1 antibody
>1,000 amino acids
~150,000 daltons
>20,000 atoms

Images not to scale.
Image and data sources:
www.jtbaker.com

Martz E. Questions on Antibody Structure. University of Massachusetts website. www.avantorinc.com . Revised January 2001. Accessed September 2018.
Genazzani AA, Biggio G, Caputi AP, et al. Biosimilar drugs : concerns and opportunities. BioDrugs. 2007;21(6):351-6.
Aspirin [comprehensive prescribing information]. Morristown, NJ: Bayer Corporation. www.fda.gov/ohrms/dockets/ac/03/briefing/4012B1_03_Appd%201-Professional%20Labeling.pdf. Accessed April 2017
Insulin, Human, Recombinant Expressed in *E. coli*. [Product information]. St. Louis, MO; Sigma-Aldrich, Inc.; 1999. www.sigmaaldrich.com/etc/medialib/docs/Sigma/Product_Information_Sheet/2/i2767pis.Par.0001.File.tmp/i2767pis.pdf. Accessed April 2017
Growth Hormone 1; GH1. OMIM website. omim.org/entry/139250. Updated January 11, 2017. Accessed April 2017. 4.
Davies DR, Padlan EA, Segal DM. *Annu Rev Biochem*. 1975;44:639-67.

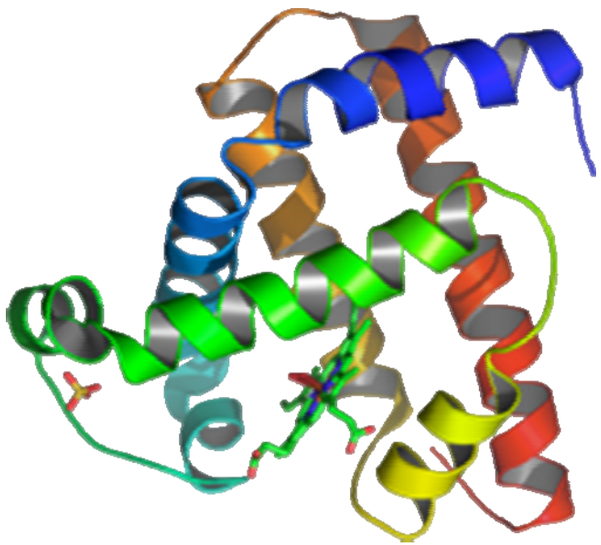
Protein Structures

alpha helices

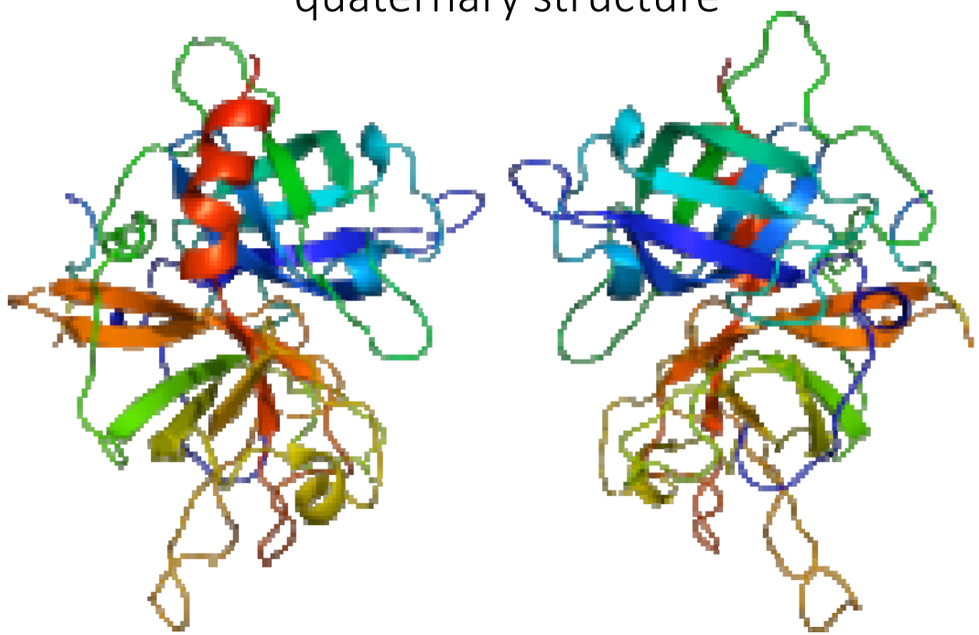


beta sheets

tertiary structure

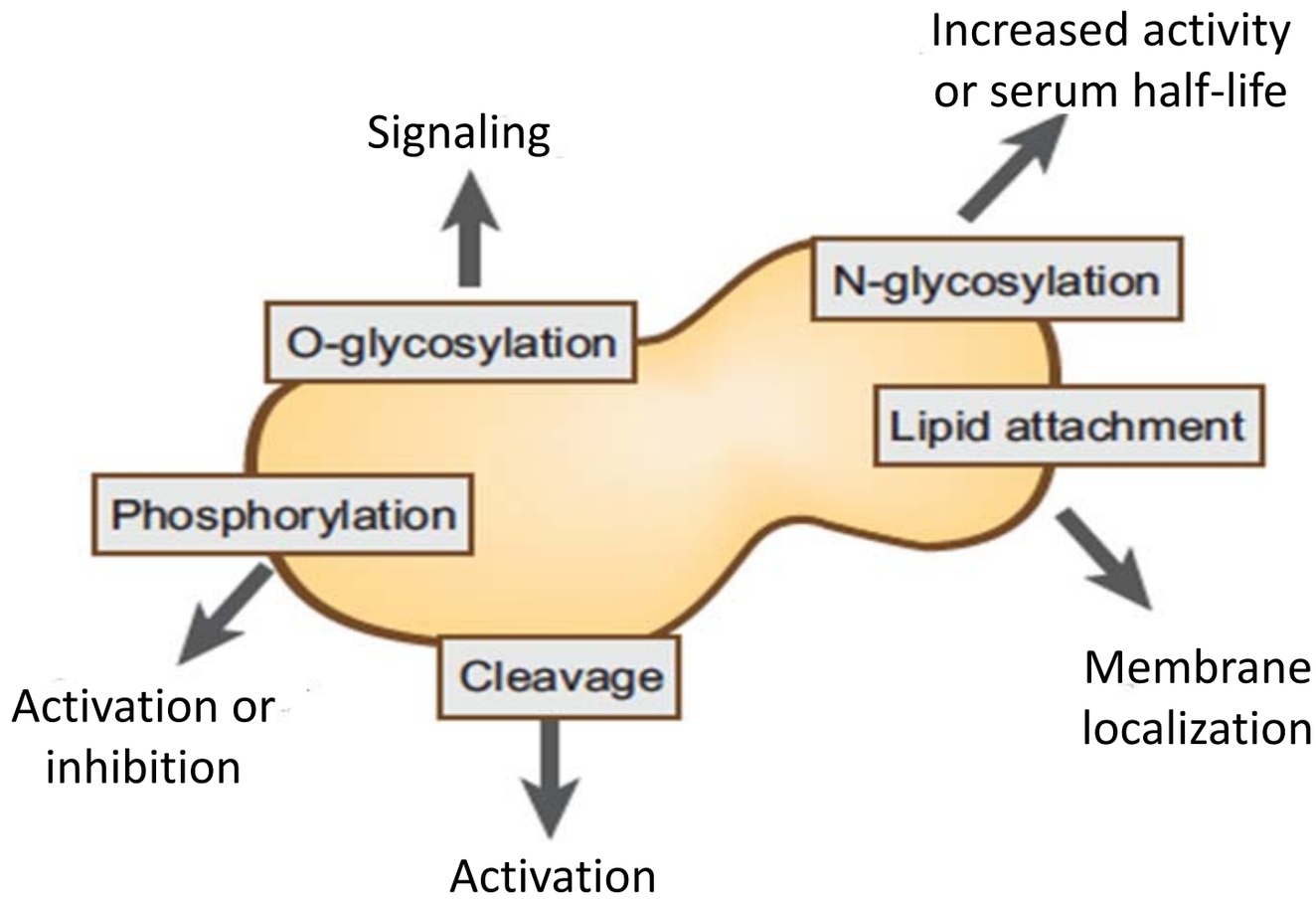


quaternary structure



What is the Impact of Post Translational Modifications (PTMs)?

- Oligomannose glycans cleared 40% faster
- Afucosylation and galactosylation independently and additively increase FcγIIIa binding [ADCC]
- Galactosylation increases and sialylation decreases C1q binding [CDC]

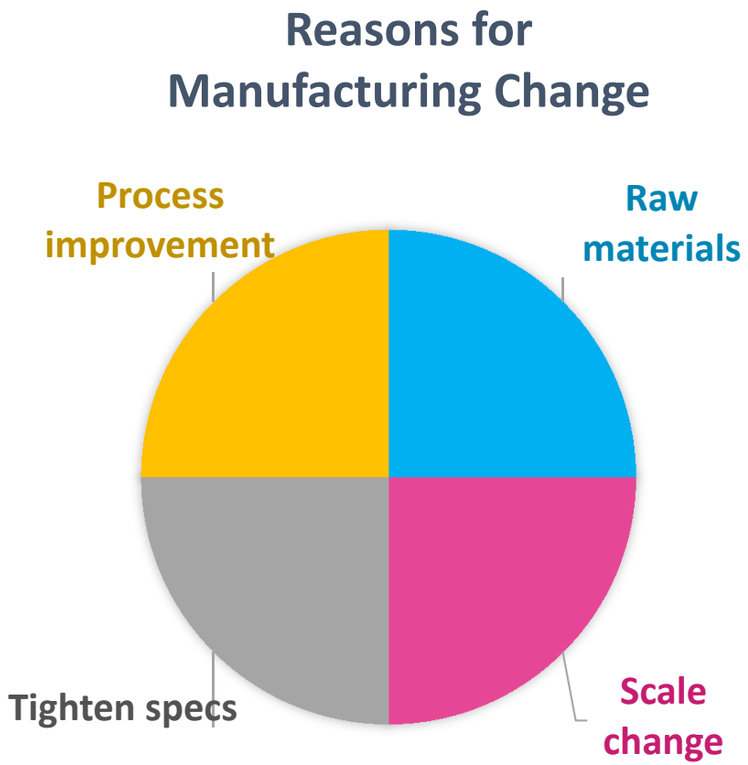


Choice of expression system and manufacturing process can impact many aspects of protein structure and function – not to mention "drift" over time

Kuhlmann M, Covic A. *Nephrol Dial Transplant*. 2006;21 Suppl 5:v4-8.

Manufacturing Changes Can Slightly Alter Physicochemical Characteristics

Reference Product	# of Changes after Approval
Infliximab	37
Etanercept	21
Adalimumab	18
Abatacept	7
Rituximab	6
Tocilizumab	4

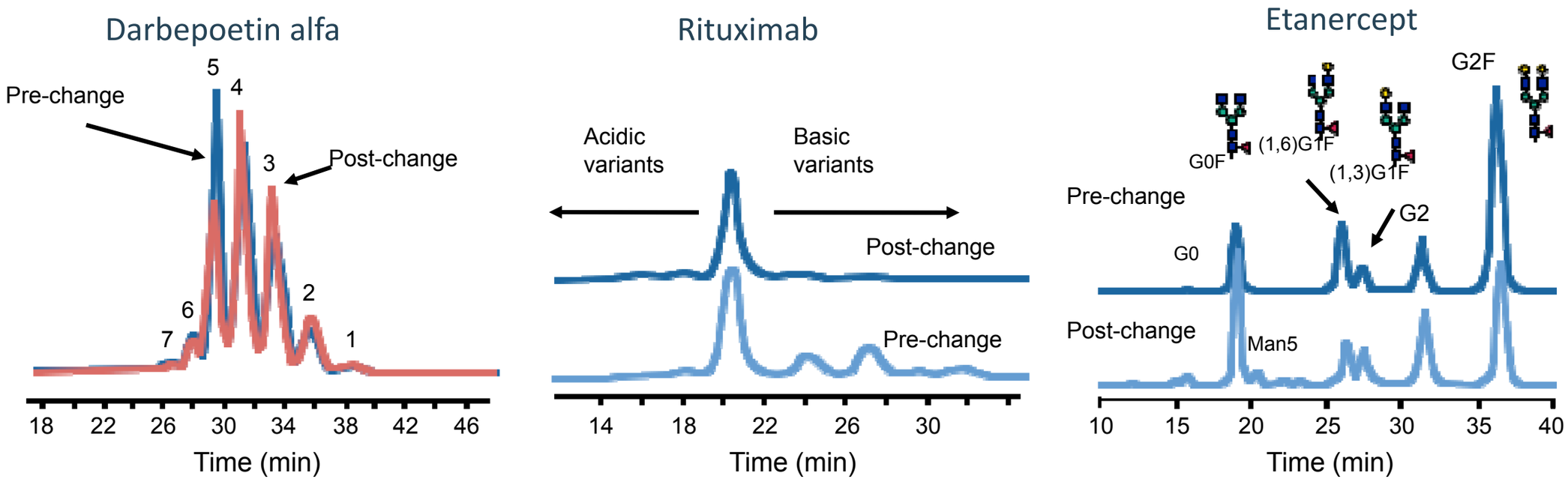


Changes made to tighten specifications and controls on the process and to increase production capacity

Schneider CK. *Ann Rheum Dis*. 2013;72(3):315-8.
Tebbey PW, Varga A, Naill M, Clewell J, Venema J. *MAbs*. 2015;7(5):805-11.

Originator Manufacturing Process Changes

- Small modifications may result in slight changes in structure

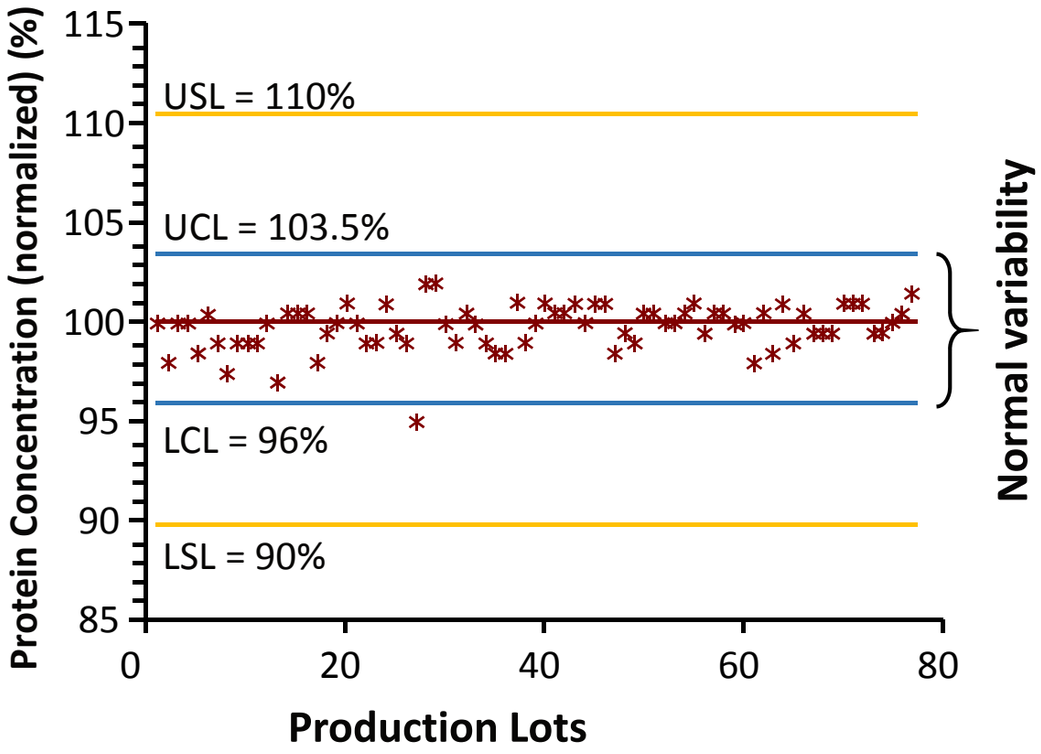


Despite these differences, when the products are within a prespecified acceptable range, the products are marketed with no change in label

Schiestl M, Stangler T, Torella C, Cepeljnik T, Toll H, Grau R. *Nat Biotechnol*. 2011;29(4):310-2.

Drift Differs from Intentional Manufacturing Changes

Example graph showing normal batch-to-batch variability for a single product attribute



USL = upper specification limit; UCL = upper control limit; LCL = lower control limit; LSL = lower specification limit.

1. Ramanan S, Grampp G. *BioDrugs*. 2014;28(4):363-72.
2. Schiestl M, Stangler T, Torella C, Cepeljnik T, Toll H, Grau R. *Nat Biotechnol*. 2011;29(4):310-2.

A tightly controlled range of attribute variation is established on basis of previous approved lots

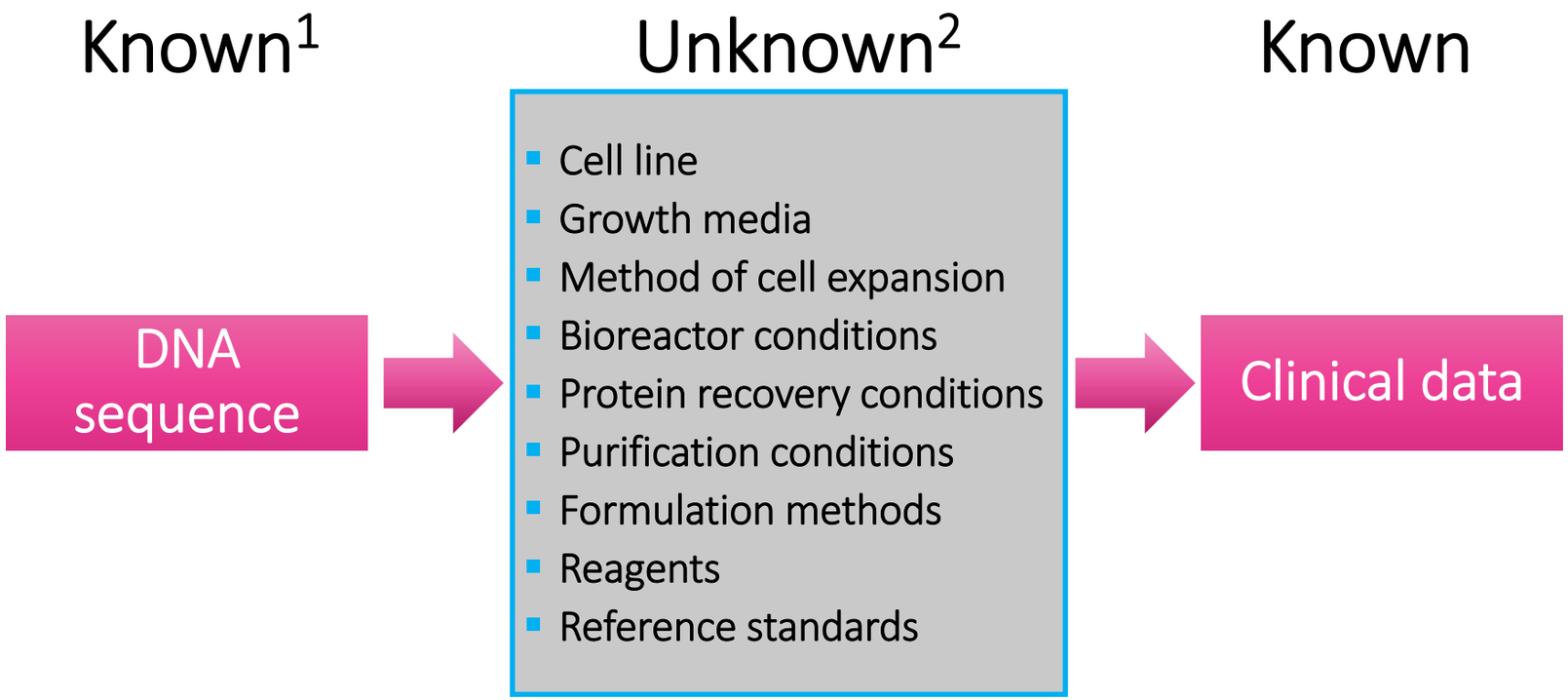
Drift

- Unintended shifting of product attributes away from their intended value
- Drift can either be a systematic trend over time in one direction or a sudden shift

Manufacturing change

- Intentional introduction of a process change

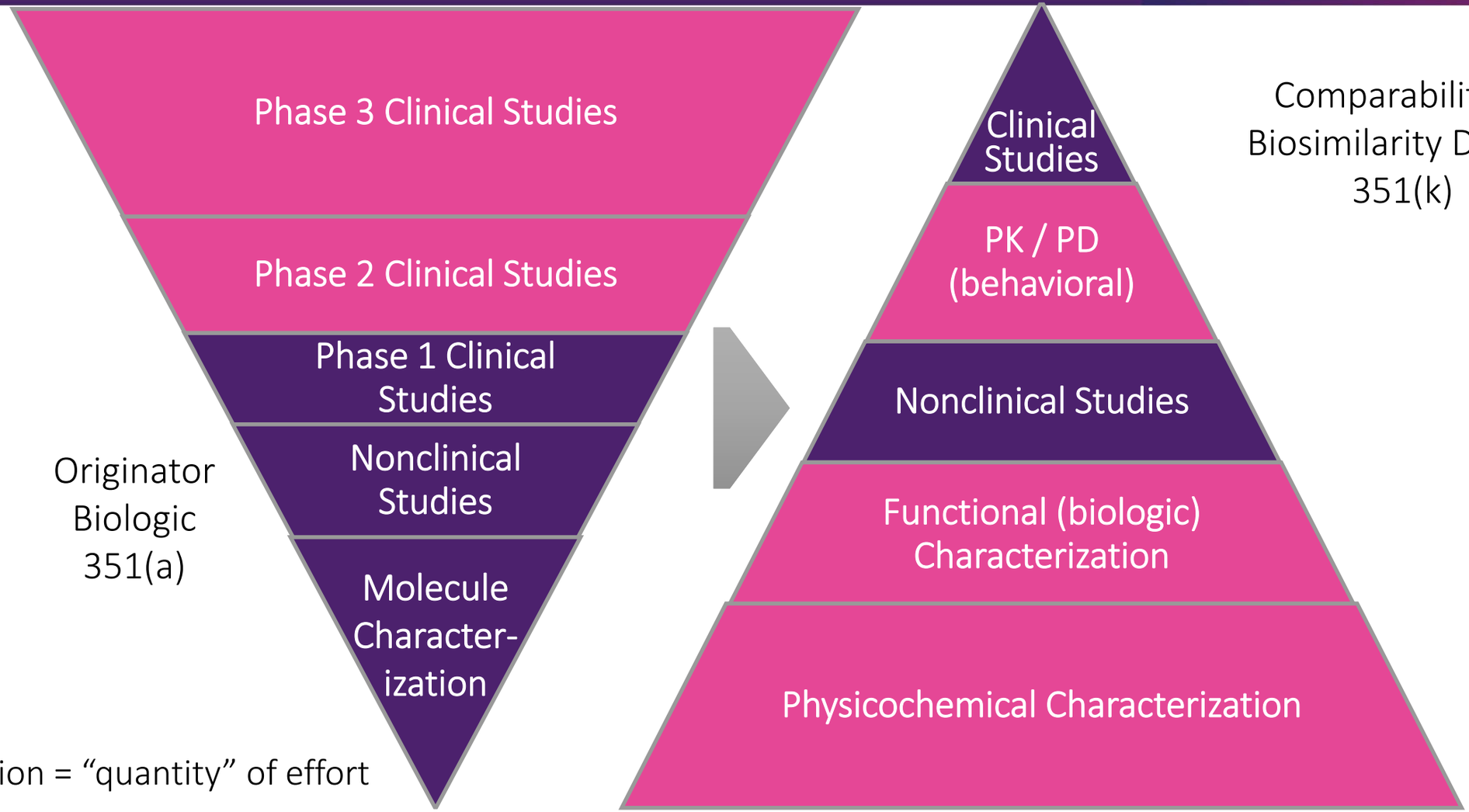
It is Impossible to Precisely Duplicate Another Manufacturer's Biologic Agent



To reverse engineer a reference product, a biosimilar developer must create a manufacturing process for that biologic de novo[2]

1. Roger SD. *Nephrology* (Carlton). 2006;11(4):341-6.
2. Mellstedt H, Niederwieser D, Ludwig H. *Ann Oncol*. 2008;19(3):411-9.

Totality of Scientific Evidence to Characterize Biosimilars



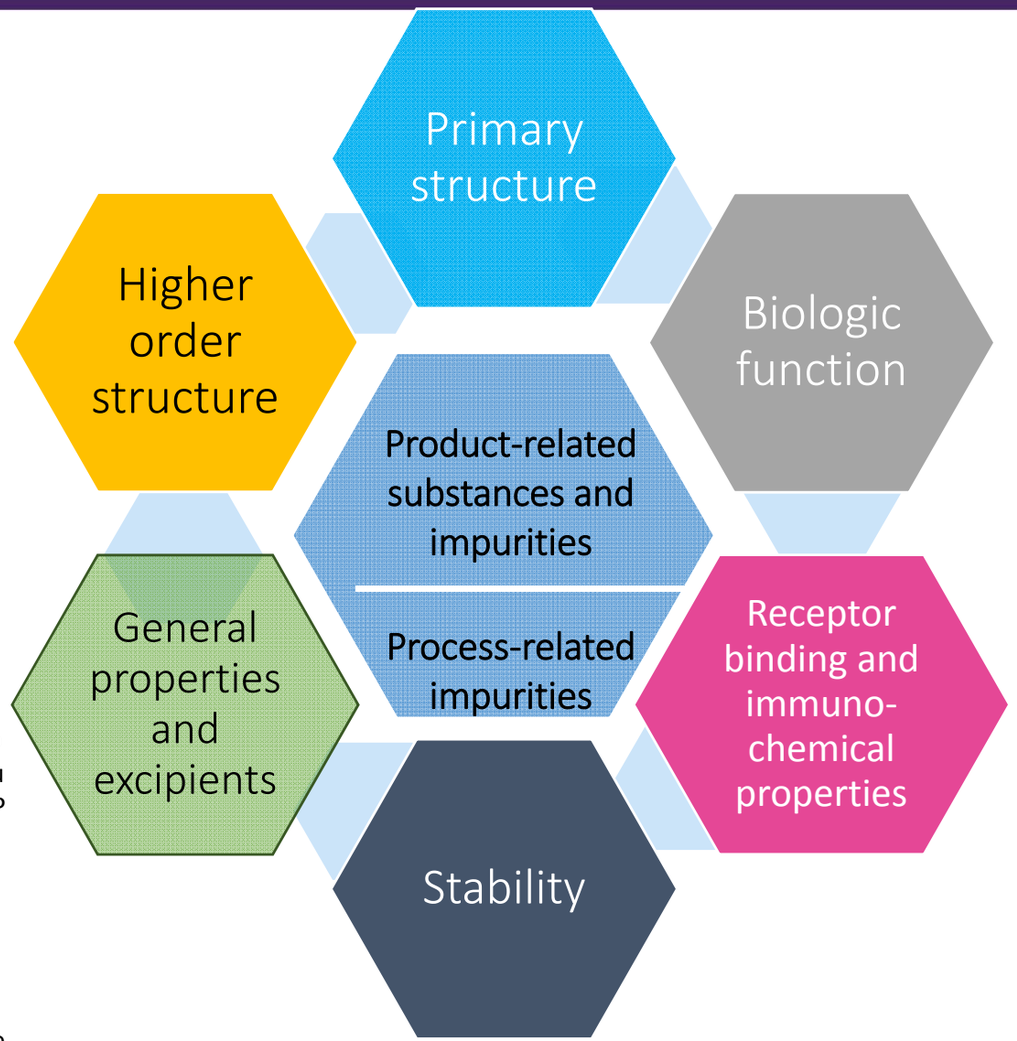
Originator Biologic 351(a)

Comparability & Biosimilarity Design 351(k)

Size of section = “quantity” of effort

“High regulatory emphasis” “Lower regulatory emphasis”

Fingerprint Analysis of Proteins



Quality Considerations for Biosimilars. FDA website archived at: http://wayback.archive-it.org/7993/20170405225927/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM315764.pdf. Published August 8, 2012. Accessed September 2018.

Quality Considerations in Demonstrating Biosimilarity of a Therapeutic Protein Product to a Reference Product. FDA website. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf. Published April 2015. Accessed April 2017.

Analytical Tools to Evaluate Proteins

- **Amino acid sequence and modifications:**
  - MS, peptide mapping, chromatographic separations
- **Folding:**
  - S-S bonding, calorimetry, HDX- and IM-MS, NMR, dyes, circular dichroism, Fourier transform spectroscopy, fluorescence
- **Subunit interactions:**
  - Chromatography, IM-MS
- **Heterogeneity of size, aggregates, charge, hydrophobicity:**
  - Chromatography resins; gel and CE, light scatter, IM-MS, analytical ultracentrifugation, size-exclusion chromatography, field flow fractionation, light scatter, microscopy
- **Glycosylation:**
  - Anion exchange, enzymatic digestion, peptide mapping, CE, MS
- **Bioactivity:**
  - Cellular and animal bioassays; ligand and receptor binding (ELISA, surface plasmon resonance), signal transduction
- **Impurities:**
  - Proteomics, immunoassays, metal and solvents analysis

MS = mass spectrometry; HDX = hydrogen/deuterium exchange; IM = ion mobility; NMR = nuclear magnetic resonance; CE = capillary electrophoresis; ELISA = enzyme-linked immunosorbent assay.

Quality Considerations for Biosimilars. FDA website archived at: http://wayback.archive-it.org/7993/20170405225927/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM315764.pdf. Published August 8, 2012. Accessed September 2018.

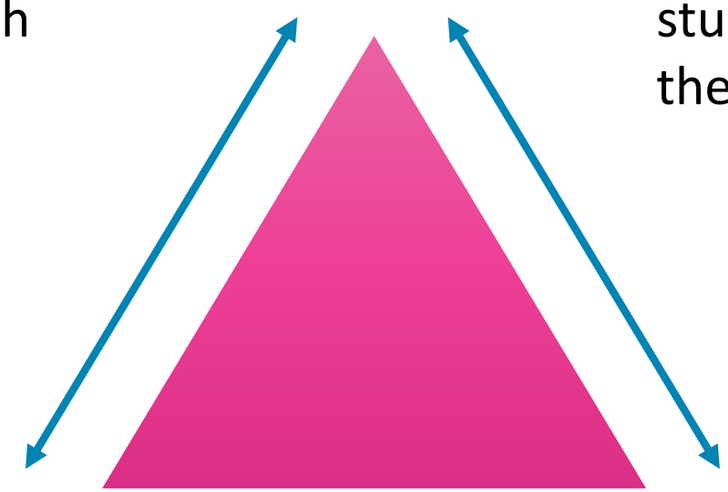
Clinical Trial Considerations for Biosimilars

Biosimilars Are Studied and Compared With the Reference Product But Are Not Tested for Similarity Compared With Other Biosimilars

Reference Biologic

Biosimilar A that has been studied in comparison with the innovator

Biosimilar B that has been studied in comparison with the innovator



Biosimilar A

Biosimilar B

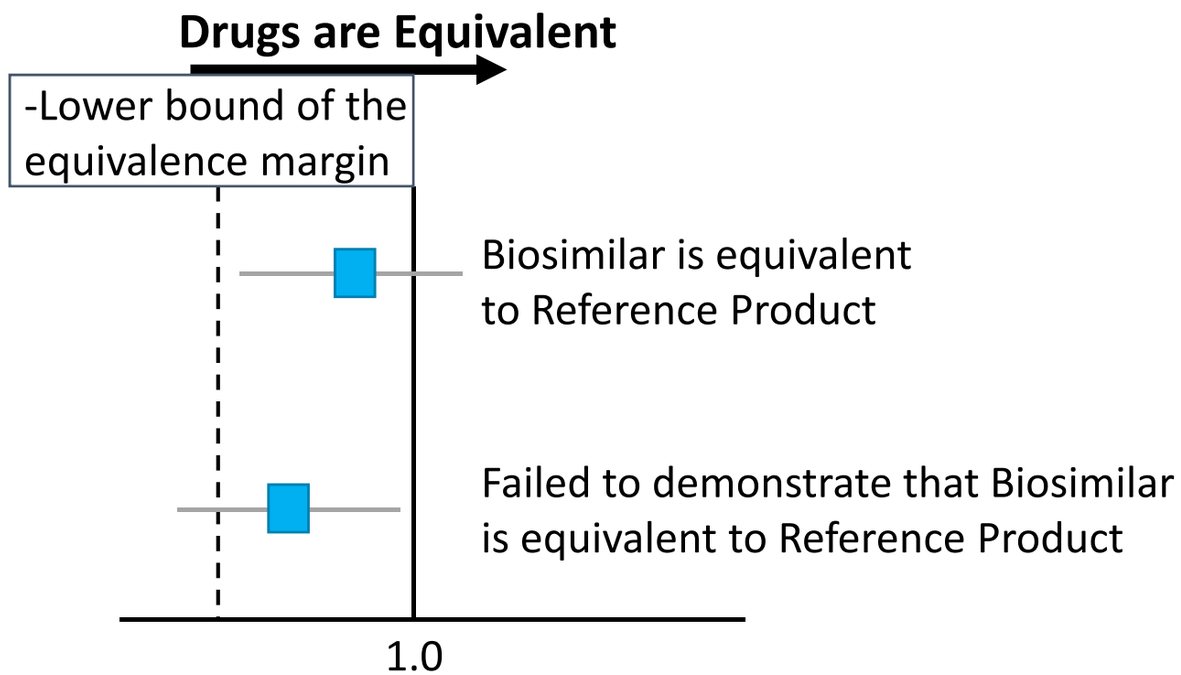
There are no comparisons between biosimilars

Pharmacokinetic Equivalency

- 2 versions of a drug are generally said to be bioequivalent if the 90% confidence intervals for the ratios of the geometric means (brand-name versus generic) of the area under the curve (AUC) and maximum concentration (C_{max}) fall within 80% and 125%
- A similar definition is applied to PK equivalency between biosimilar and reference product
  - Clinical PK similarity on all 3 required, prospectively defined, PK endpoints, with **all 3 geometric mean ratios fully within the 90% CI from 80–125%**
    - Maximum serum concentration (C_{max})
    - Area under the time-concentration curve from 1st to last time point measured (AUC_{0-t}), and
    - Area under the time-concentration curve from 1st time point extrapolated to infinity ($AUC_{0-¥}$)
- PD equivalence studies are also required (specific studies determined by FDA with biosimilar manufacturers)

Understanding Biosimilar Clinical Trials

- Efficacy and safety: specific clinical trial design will depend on which residual questions remain
  - Clinical studies should be designed to demonstrate neither decreased nor increased activity
  - Use clinically relevant and sensitive endpoints in a sensitive population
  - Biosimilar sponsor to justify comparability delta



Schellekens H. *NDT Plus*. 2009;2(Suppl_1):i27-i36.

Understanding Biosimilar Clinical Trials

- A clinical study or studies sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions for which the reference product is licensed
- Equivalence/noninferiority vs. superiority
- Must be clinically meaningful
  - Study size and design sufficient to detect clinically meaningful differences
- Sensitive (do PD measures correlate with clinical outcomes?)
- Other considerations
  - Understanding of MOA of the biologic
  - Extrapolation

Goal is not to demonstrate that the biosimilar is safe and effective, but to determine if there are differences compared to the reference

- Use clinically **relevant and sensitive endpoints** in the right population

Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. FDA website. http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf. Published April 2015. Accessed September 2018.

Superiority vs Equivalence: Study Design and Interpretation

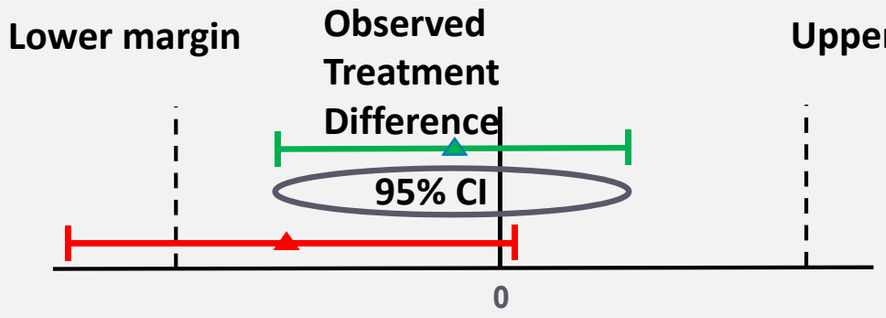
Superiority study: new treatment "N" is different from standard "S"?

***P* value < 0.05**

***P* value > 0.05**

Confidently (at least 95% certainty) claim that treatment N is significantly different than standard S.

Equivalence study: biosimilar "B" is similar to reference product "R"?



Confidently (at least 95% certainty) claim that treatment B is clinically similar to reference product R.

Pater C. *Curr Control Trials Cardiovasc Med*. 2004;5(1):8.

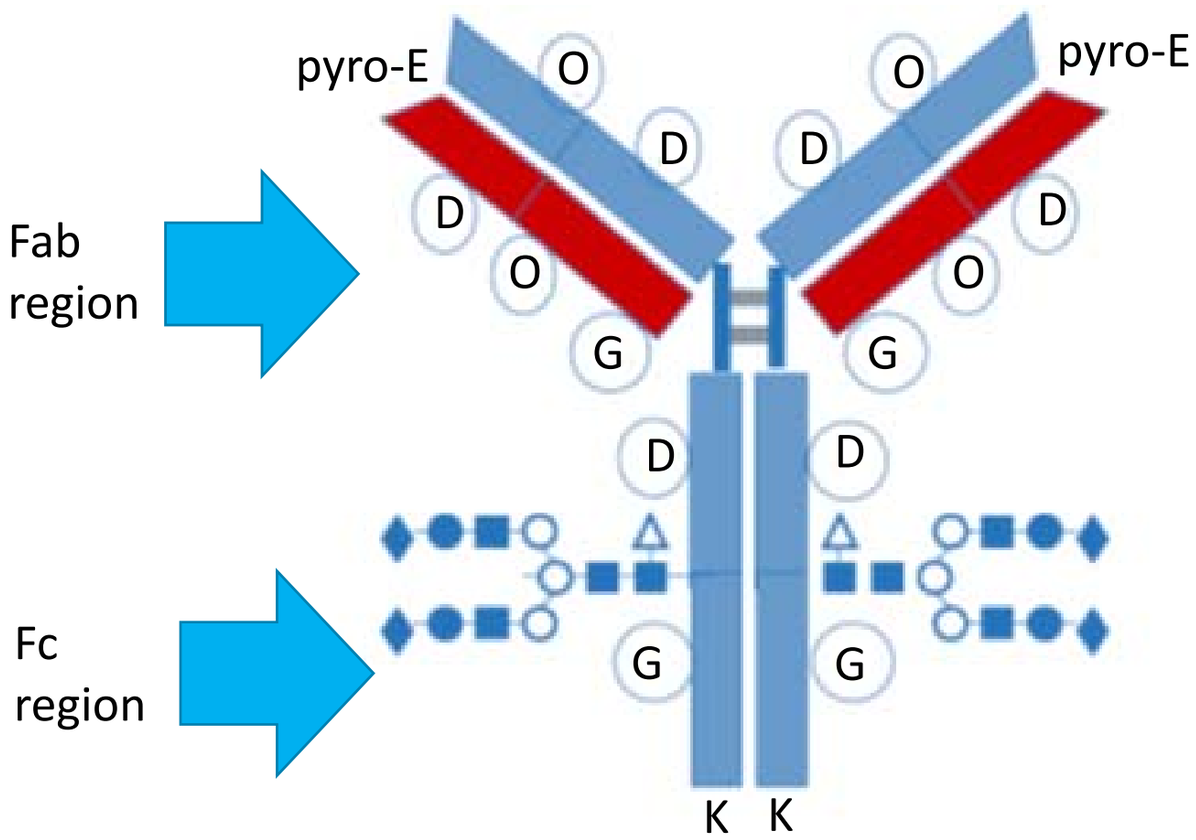
Indication Extrapolation

- One of most contentious issues about regulatory approval process
- Factors
  - Knowledge of MOI in each indication
  - Knowledge of target receptors
  - Product structure and target receptor interactions
  - PK in different patient populations
  - Immunogenicity profile between indications

All biosimilars approved to date in EU and US have had indications extrapolated to all eligible indications

Weise M, Kurki P, Wolff-holz E, Bielsky MC, Schneider CK. *Blood*. 2014;124(22):3191-6.
Christl, L. FDA's Overview of the Regulatory Guidance for the Development and Approval of Biosimilar Products in the US. www.fda.gov/downloads/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/therapeuticbiologicapplications/biosimilars/ucm428732.pdf. Accessed November 14, 2017.

Monoclonal Antibody Overview
Fab vs. Fc regions



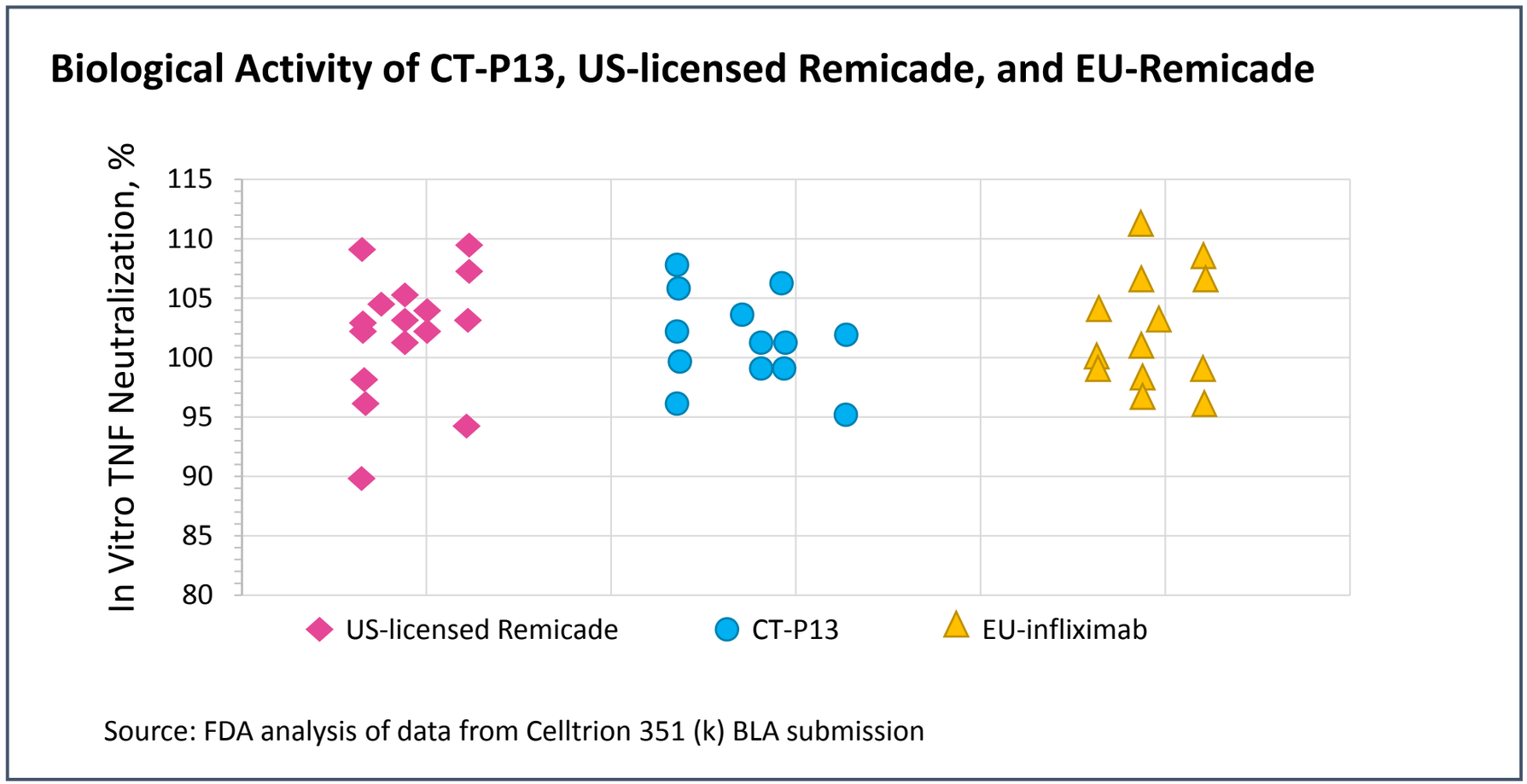
- ***Chemical modifications***
  - *Pryo-Glutamate (2)*
  - *D = Deamidation (3 x 2)*
  - *O = Methionine oxidation (2 x 2)*
  - *G = Glycation (2 x 2)*
- ***Biosynthetic or enzymatic modifications***
  - *High mannose, G0, G1, G1, G2 (5)*
  - *Sialylation (5)*
  - *K = C-terminal Lysine (2)*

$(9{,}600)^2 \approx 10^8$

$2 \times 6 \times 4 \times 4 \times 5 \times 5 \times 2 = 9{,}600$

Kozlowski S, Swann P. *Adv Drug Deliv Rev*. 2006;58(5-6):707-22.

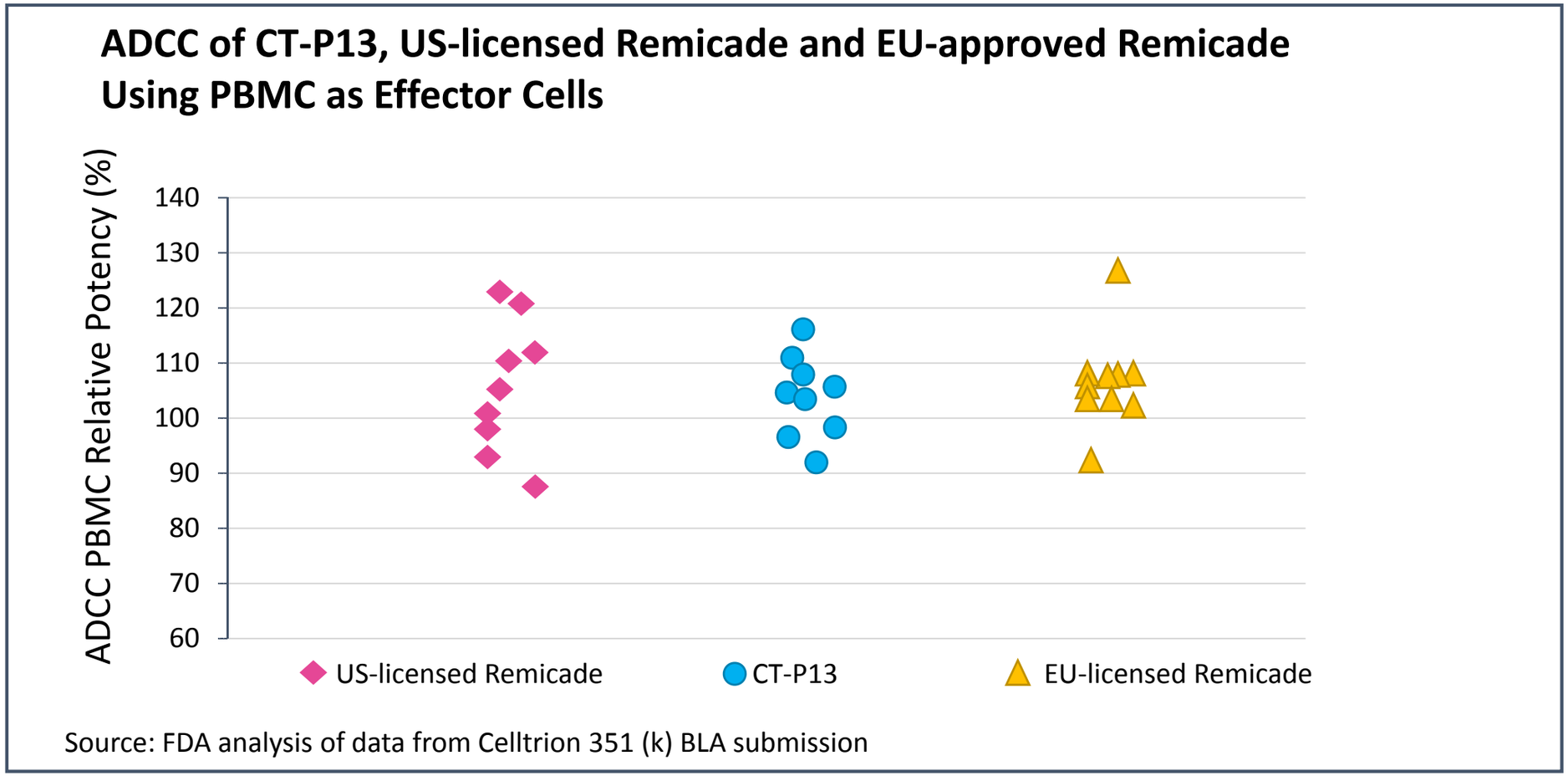
TNF-alpha Neutralization (Fab region)



Source: FDA analysis of data from Celltrion 351 (k) BLA submission

FDA Briefing Document: Arthritis Advisory Committee Meeting. FDA website. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM484859.pdf. Accessed September 2018.

What Difference in ADCC? (FC Region)



Source: FDA analysis of data from Celltrion 351 (k) BLA submission

ADCC – antibody-dependent cellular cytotoxicity
PBMC – Peripheral blood mononuclear cells

FDA Briefing Document: Arthritis Advisory Committee Meeting. FDA website. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM484859.pdf. Accessed September 2018.

Fc binding in Crohn's Disease and Ulcerative Colitis?

Known and Potential (Likely or Plausible) Mechanisms of Action of US-licensed Remicade in the Licensed Conditions of Use

MOA of Remicade	RA	AS	PsA	PsO	CD, Pediatric CD	US, Pediatric UC
Mechanisms involving the Fab (antigen binding) region:						
Blocking TNFR1 and TNFR2 activity via binding and neutralization of s/tmTNF	Known	Known	Known	Known	Likely	Likely
Reverse (outside-to-inside) signaling via binding to tmTNF:	-	-	-	-	Likely	Likely
Apoptosis of lamina propria activated T cells	-	-	-	-	Likely	Likely
Suppression of cytokine secretion	-	-	-	-	Likely	Likely
Mechanisms involving the Fc (constant) region:						
Induction of CDC on tmTNF- expressing target cells (via C1q binding)	-	-	-	-	Plausible	Plausible
Induction of ADCC on tmTNF- expressing target cells (via FcγRIIIa binding expressed on effector cells)	-	-	-	-	Plausible	Plausible
Induction of regulatory macrophages in mucosal healing	-	-	-	-	Plausible	Plausible
ADCC: antibody-dependent cellular cytotoxicity; AS: ankylosing spondylitis; CD: Crohn's Disease; CDC: complement-dependent cytotoxicity; MOA mechanism of action; PsA: psoriatic arthritis; PsO: plaque psoriasis; RA: rheumatoid arthritis; US: ulcerative colitis; sTNF: soluble TNF; tmTNF: transmembrane TNF						

Source: FDA summary of existing literature on the topic of mechanisms of action of US-licensed Remicade[8,9]

FDA Briefing Document: Arthritis Advisory Committee Meeting. FDA website.

What was FDA's Conclusion?

- "The mechanism of action of TNF inhibitors in treating IBD is complex and,…ADCC is only one of the several plausible mechanisms of action. It is noteworthy that products without any ADCC capability have been approved for the treatment of Crohn's Disease (i.e. certolizumab)…"
- "… has provided data to demonstrate analytical similarity in all other potential mechanisms of action of infliximab in IBD."
- "Therefore, based on the above considerations, it is **reasonable to extrapolate conclusions regarding similar efficacy and safety of CT-P13 and US-licensed Remicade to IBD."**

FDA Briefing Document: Arthritis Advisory Committee Meeting. FDA website. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM484859.pdf. Accessed September 2018.

Indication Extrapolation Example (Infliximab-dyyb)

Indication	Remicade	Inflectra
Rheumatoid arthritis (in combination with methotrexate)	Yes	Yes
Ankylosing spondylitis	Yes	Yes
Psoriatic arthritis	Yes	**Yes***
Plaque psoriasis	Yes	**Yes***
Crohn's Disease	Yes	**Yes***
Pediatric Crohn's Disease	Yes	**Yes***
Ulcerative Colitis	Yes	**Yes***
Pediatric Ulcerative Colitis (orphan)	Yes	No

***Extrapolated indication**

Inflectra (infliximab-dyyb; Celltrion/Pfizer) [package insert]. New York, NY: Pfizer; August 2016. https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/125544s000lbl.pdf
FDA Briefing Document: Arthritis Advisory Committee Meeting. FDA website.
http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM484859.pdf. Accessed September 2018.

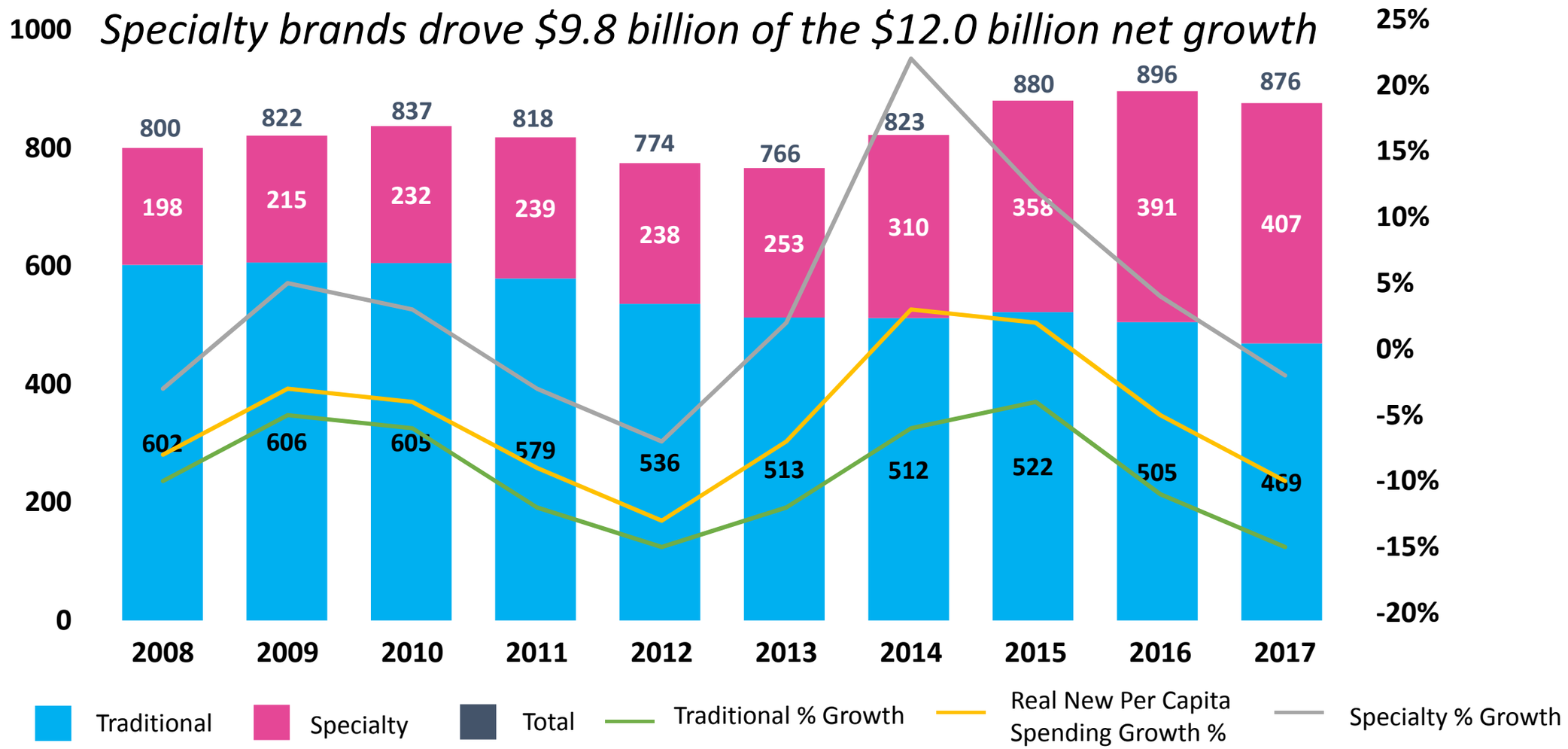
Summary

- The Biologics Price Competition and Innovation Act (BPCIA) of 2009 created an abbreviated licensure pathway for biological products, with continued guidance being issued by FDA
- Under BPCIA, a biological product may be demonstrated to be “biosimilar” if data show that the product is “highly similar” to an already-approved biological product (the “reference” product)
- Adoption of biosimilars in the US currently lags the rest of the developed world; however, by 2020, it is anticipated that several more “innovator” or “reference” biologics will lose patent protection
- Biosimilars present an opportunity to improve patient accessibility to biologic therapies and reduce the cost of treatment

Addressing Challenges for Managed Care Posed by Biosimilars

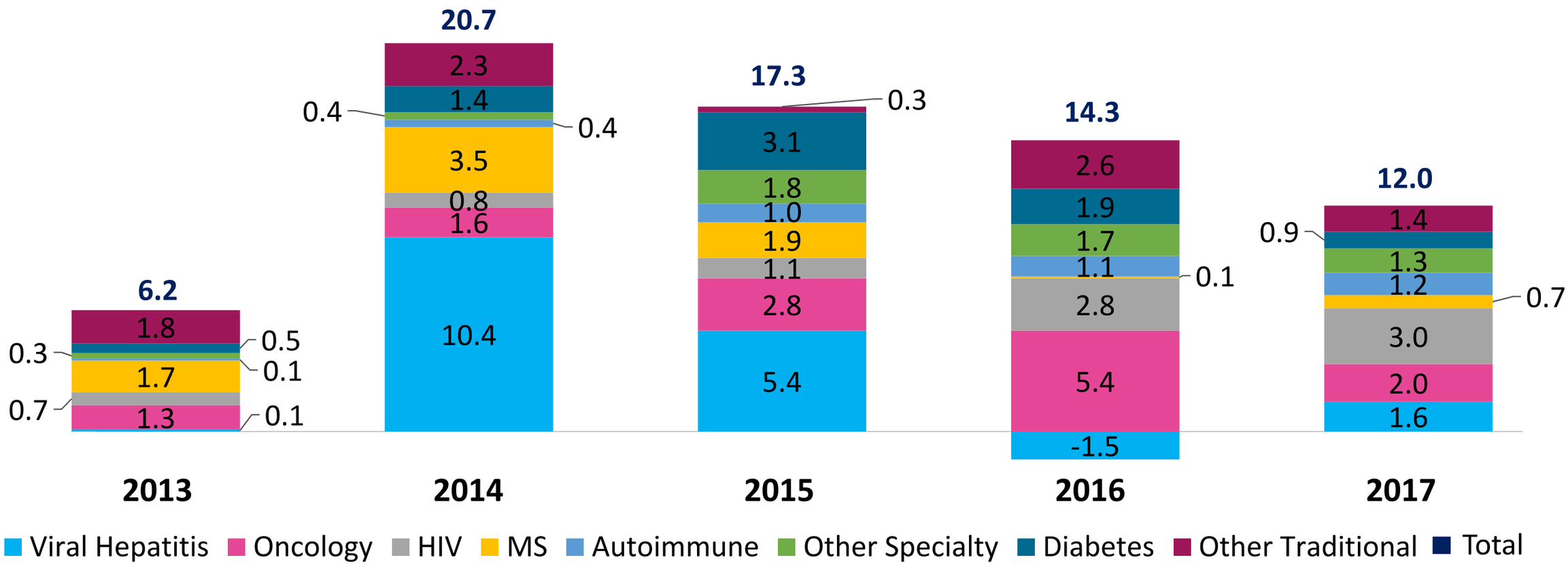
Edmund Pezalla, MD, MPH
CEO
Enlightenment Bioconsult, LLC

Traditional Pharmaceutical Spending is Being Outpaced and Replaced by Specialty Spending



Medicine Use and Spending in the U.S. IQVIA Institute for Human Data Science. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us-a-review-of-2017-and-outlook-to-2022.pdf?_=1532281287705 Published April 2018. Accessed September 2018.

Oncology and Autoimmune Conditions are Key Drivers of the Specialty Trend and Represent Areas of Significant Biosimilar Development



Source: IQVIA National Sales Perspectives, IQVIA Institute, Dec. 2017

Medicine Use and Spending in the U.S. IQVIA Institute for Human Data Science. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us-a-review-of-2017-and-outlook-to-2022.pdf?_=1532281287705 Published April 2018. Accessed September 2018.

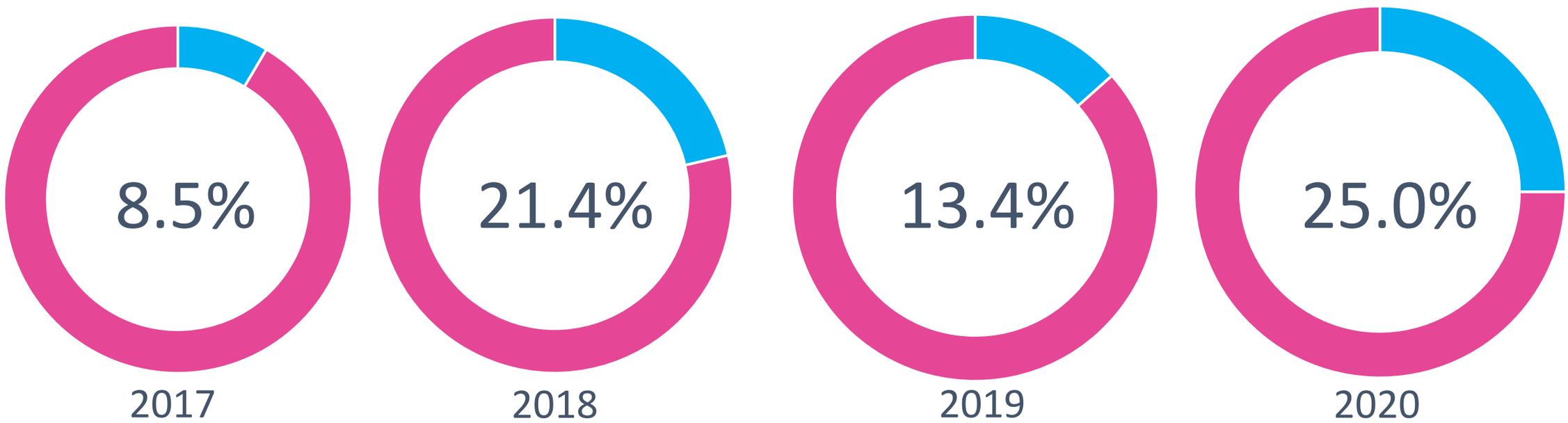
Biosimilars Represent Mounting Competition in the Specialty Biologics Market

- In 2018, $19 billion of spending on biologics will become exposed to competition from biosimilars for the first time in 1 or more developed markets worldwide
  - Compared to $3 billion that became exposed in 2017, and adding to the $26 billion already facing competition
  - New exposure to competition in 2018 is the largest single-year change to date
- In the period from 2019 to 2022, $52 billion is expected to face biosimilar competition for the first time in developed countries
  - The US market comprises $37 billion of this competition
- 77% of current spending on biologics will be subject to competition by 2027
- Between 2018 and 2022, competition from biosimilars could bring down spending on biologics by 10% to 30% or by $50 billion to $78 billion
- However, spending on biosimilars will depend on factors such as the number of competitors, the speed with which competition enters the market, and the extent to which biosimilars compete on price

Medicine Use and Spending in the U.S. IQVIA Institute for Human Data Science. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us-a-review-of-2017-and-outlook-to-2022.pdf?_=1532281287705 Published April 2018. Accessed September 2018.

A Quarter of Health Care Stakeholders Expect Biosimilars to Reduce Drug Spending by 2020

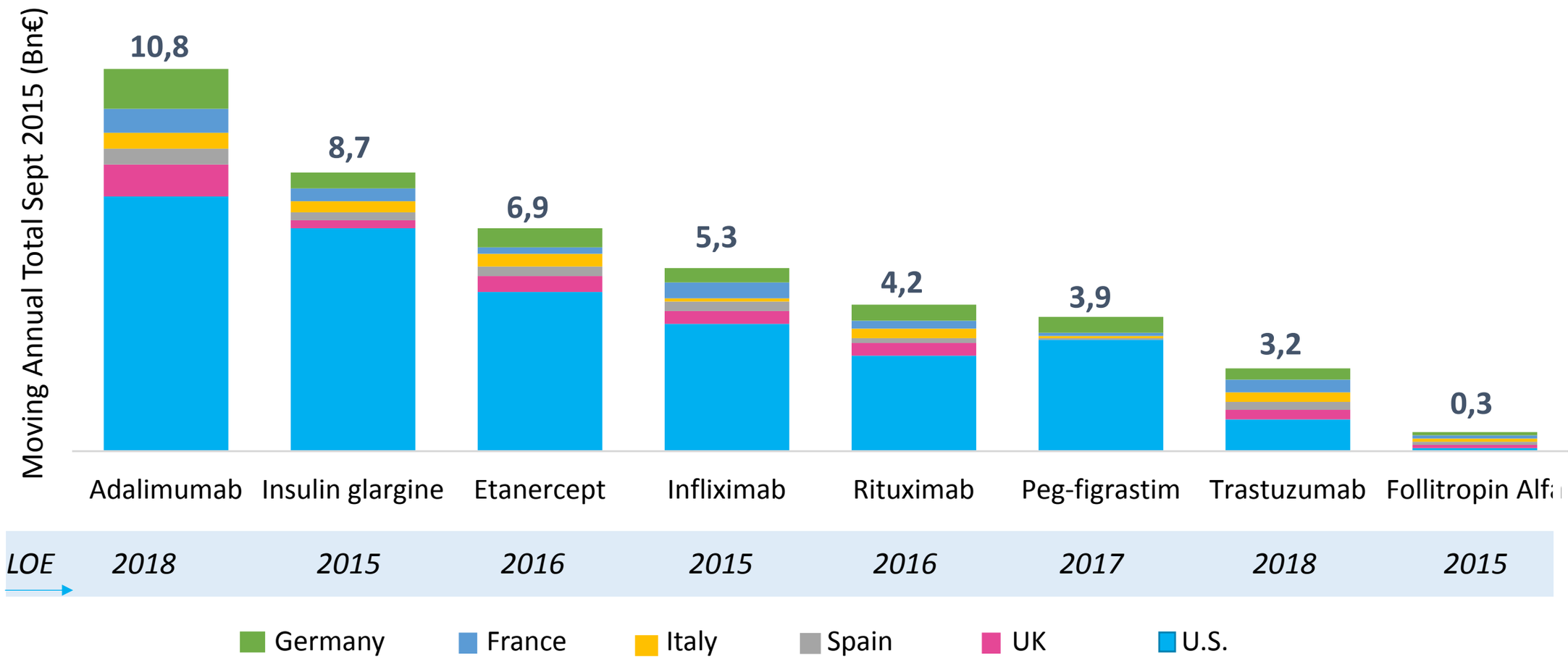
Percentage of Respondents Who Foresee Biosimilars Reducing Drug Spend for Specialty Drugs in Coming Years



N=228 executives at medical practices, hospitals, large health care systems, benefit management organizations, health plans, long-term care organizations, group purchasing organizations and consulting firms

Appold, K. *Managed Healthcare Executive*. 2016;26:1-36.

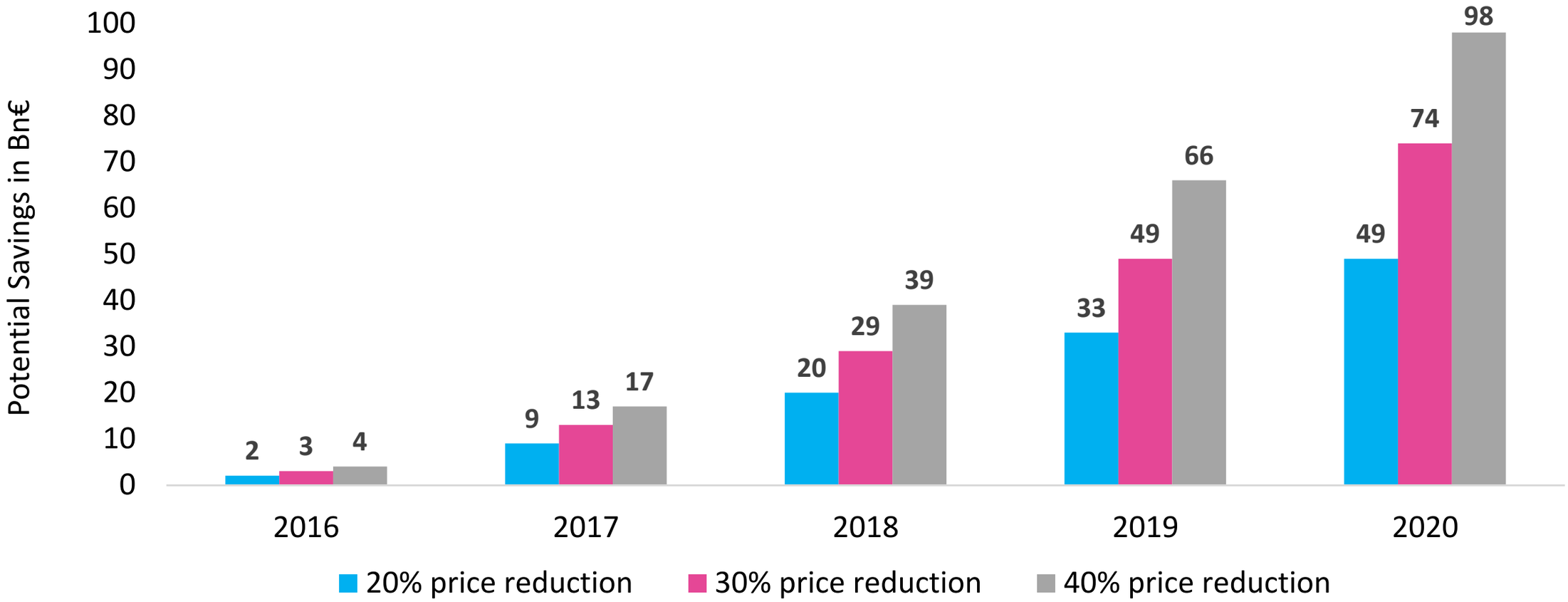
European and US Sales of Key Biologics Scheduled to Lose Patent Protection in 2015-2020



Source: IMS Health, MIDAS, Dec 2015

Delivering on the Potential of Biosimilar Medicines. IMS Institute for Healthcare Informatics. https://www.medicinesforeurope.com/wp-content/uploads/2016/03/IMS-Institute-Biosimilar-Report-March-2016-FINAL.pdf March 2016. Accessed September 2018.

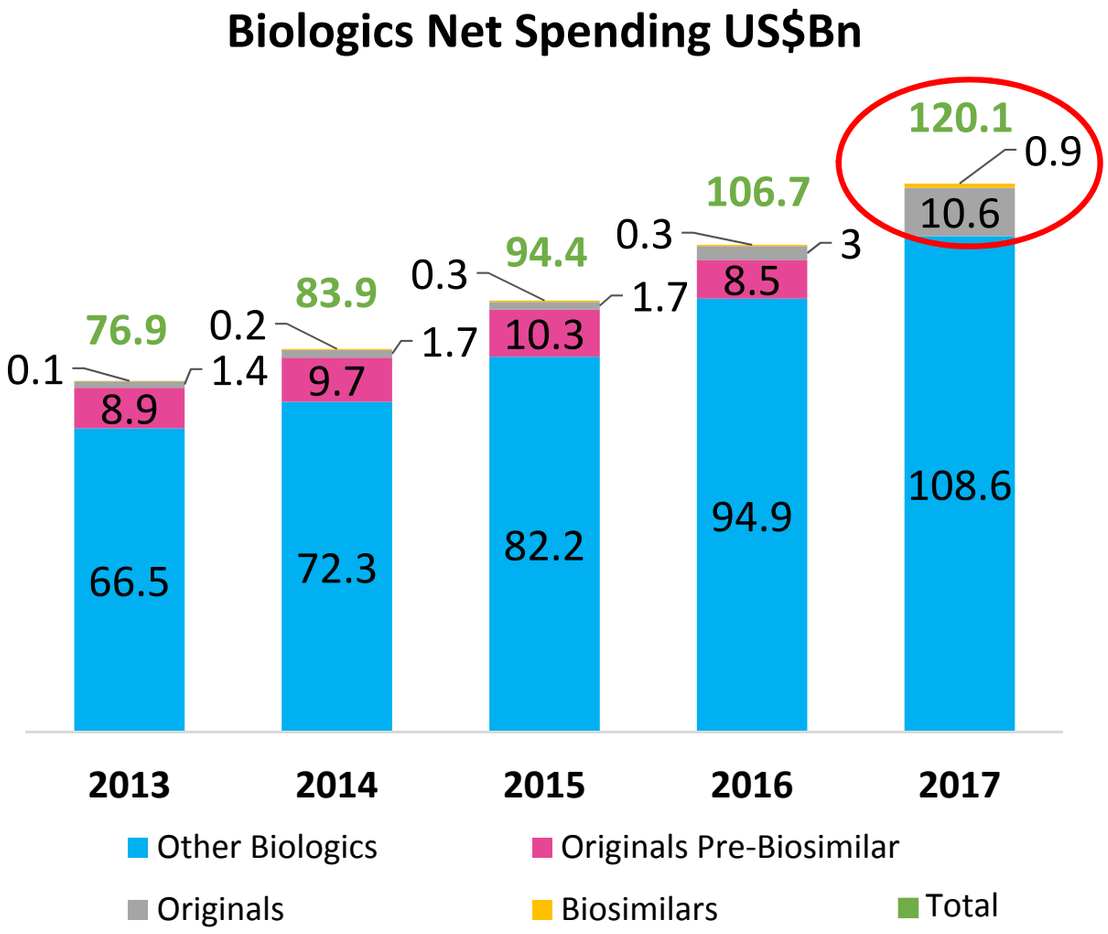
Biosimilar Savings Potential in Europe and the US for 8 Key Products in 2015-2020

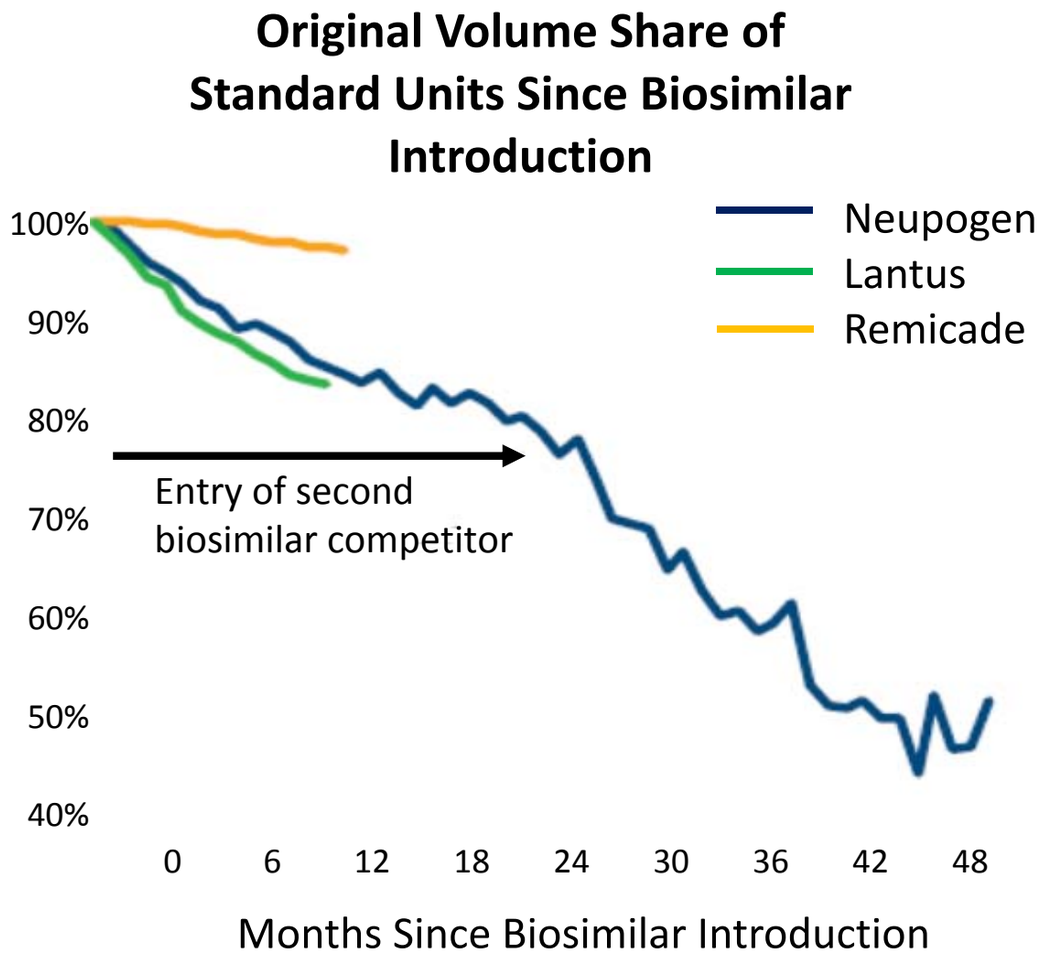


Source: IMS Health, MIDAS, IMS Health Market Prognosis; IMS Institute for Healthcare Informatics, Dec 2015

Delivering on the Potential of Biosimilar Medicines. IMS Institute for Healthcare Informatics. https://www.medicinesforeurope.com/wp-content/uploads/2016/03/IMS-Institute-Biosimilar-Report-March-2016-FINAL.pdf March 2016. Accessed September 2018.

Biologics compete for Market Share Among Medicines with $11.5 Billion in Spending





Medicine Use and Spending in the U.S. IQVIA Institute for Human Data Science. https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/medicine-use-and-spending-in-the-us-a-review-of-2017-and-outlook-to-2022.pdf?_=1532281287705 Published April 2018. Accessed September 2018.

Ascertaining the Impact of Biosimilars on Payer Operations

- The anticipated access and financial benefits of biosimilars must be reconciled with relative unfamiliarity associated with these agents
- Generally speaking, knowledge is limited with respect to the following:
  - Manufacturing processes
  - Clinical features
  - Regulatory requirements
- Prescribing biosimilars is currently a novelty in many clinical practice settings in the US
  - Thus, payers will face specific operational challenges associated with uptake and use of these drugs

Gray N. *BioPharrmaDive*. https://www.biopharmadive.com/news/why-inflectra-may-face-greater-challenges-than-zarxio-in-winning-over-us-do/418206/ Published April 27, 2016. Accessed September 2018.

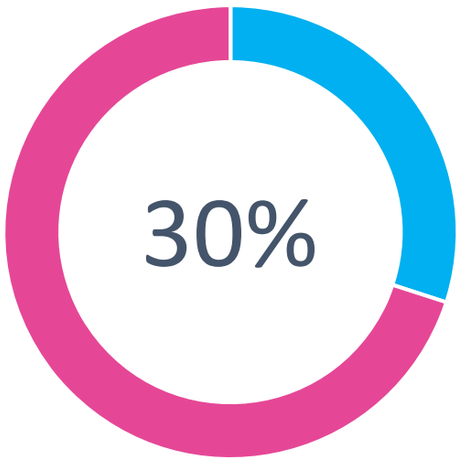
Operational Challenges for Payers

- Product substitution
- Formulary management
- Order management and information systems
- Supply chain
- Financial considerations
- Education

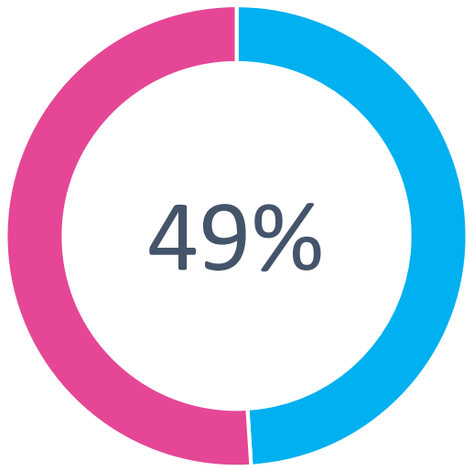
Welch AR. *Biosimilar Development*. https://www.biosimilardevelopment.com/doc/biosimilar-questions-the-payer-perspective-part-0001. June 27, 2017. Accessed September 2018.
Welch AR. *Biosimilar Development*. https://www.biosimilardevelopment.com/doc/biosimilar-questions-the-payer-perspective-part-0002. June 29, 2017. Accessed September 2018.

Product Substitution

Widespread adoption of biosimilars is not immediately anticipated, raising the issue of product substitution



Physicians likely to alter a patient's treatment regimen if he/she is stable on the current branded therapy



Physicians anticipate prescribing biosimilars for treatment-naïve patients

N=150 dermatologists, endocrinologists, gastroenterologists, oncologists, and rheumatologists

InCrowd. MicroSyndicated Study: Biosimilar Perceptions & Expectations. https://incrowdnow.com/press-release/nearly-half-of-us-physicians-say-they-will-prescribe-more-biosimilars-according-to-new-data-from-incrowd/ Published February 10, 2016. Accessed September 2018.

Product Substitution

Biosimilarity does *not* automatically confer interchangeability

BIOSIMILIARITY

- **Highly similar,** notwithstanding minor differences in clinically inactive components
- **No clinically meaningful differences in safety**, purity, and potency of the product

INTERCHANGEABILITY

Approved as a biosimilar AND:

- **Expectation of same clinical result** as the reference product in any given patient; and
- For a product that is administered more than once, **no additional risk to safety or efficacy** as a result of alternating or switching

FDA.gov. Biologics Price Competition and Innovation Act of 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf. Updated March 23, 2010. Accessed September 2018.
2016 Trends in Biosimilars Report. Amgen website. http://www.amgenbiotech.com/resources/2016_Amgen_Trends_in_Biosimilars_Report_USA-BIO-122466.pdf. Published 2016. Accessed September 2018.

Product Substitution

- An interchangeable designation requires additional evidence beyond that required for FDA approval as a biosimilar
- Receiving this designation means that a biosimilar may be substituted for the reference product at the retail or specialty pharmacy without the intervention of the prescriber in states that have approved legislation or regulation establishing state standards for biosimilar substitution
- Per the FDA draft guidance document on interchangeability, the Agency expects the following:
  - At least one switching study involving three or more switches between the biosimilar and its US-licensed reference product
  - Data showing that the biosimilar can be expected to produce the same clinical result as the reference product in all of the reference product's conditions of use

FDA.gov. Biologics Price Competition and Innovation Act of 2009. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/UCM216146.pdf. Updated March 23, 2010. Accessed September 2018.
National Conference of State Legislatures. Available at: http://www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-ofbiosimilars.aspx. Accessed September 2018
FDA.gov. Considerations in Demonstrating Interchangeability With a Reference Product.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf. Published January 2017. Accessed September 2018.

Formulary Management

- Fewer than half of the biosimilars approved in the US are currently available on the market
- The first four approved biosimilars in the US received approval for all available (i.e., non-orphan) indications
  - However, some indications may be initially excluded from an approved biosimilar's label due to FDA-established exclusivity periods
- Although plan formulary might continue covering a biosimilar for the larger patient populations, formularies will need to keep some kind of relationship with the reference product manufacturer to cover those orphan indications

2016 Trends in Biosimilars Report. Amgen website. http://www.amgenbiotech.com/resources/2016_Amgen_Trends_in_Biosimilars_Report_USA-BIO-122466.pdf. Published 2016. Accessed September 2018.

Formulary Management

Evaluating Biosimilars from a Formulary Perspective

Clinical Considerations

- Indications
- Safety and efficacy according to available data
- Immunogenicity

Product Considerations

- Nomenclature
- Manufacturing and supply chain
- Packaging, labeling, and storage

Institutional Considerations

- Substitutions and interchangeability
- Therapeutic interchange
- Transition of care
- Pharmacovigilance
- Cost
- Reimbursement
- Provider and patient education
- Information technology

Ventola CL. *P T*. 2015;40:680–689.

Order Management and Information Systems

- Information technology (IT) systems must be adapted to accurately manage and track biosimilars
- This process will likely involve changes to ensure capabilities of distinguishing between multiple versions of biologic products and biosimilars
- The system must be able to accurately track and trace product preference, conversions, utilization, and reported adverse events, as well as identify specific products for reimbursement and rebate tracking

2016 Trends in Biosimilars Report. Amgen website. http://www.amgenbiotech.com/resources/2016_Amgen_Trends_in_Biosimilars_Report_USA-BIO-122466.pdf. Published 2016. Accessed September 2018.

Order Management and Information Systems

- Systems may need to be reprogrammed to support various coding and pricing schemes, and to account for new insurance authorizations for different HCPCS codes
- Evaluation of the potential costs associated with making needed IT system changes in addition to the total cost of full formulary conversion to a biosimilar may be compared to potential savings to help determine if a change will be beneficial in the short- and long-term

2016 Trends in Biosimilars Report. Amgen website. http://www.amgenbiotech.com/resources/2016_Amgen_Trends_in_Biosimilars_Report_USA-BIO-122466.pdf. Published 2016. Accessed September 2018.

Supply Chain

- Payers rely on specialty pharmacy providers (SPPs) to enhance the efficiency of biologics distribution with respect to issues such as inventory management, product dating, product storage, cost, and delivery
- Contracted SPPs must remain knowledgeable and take precautions with respect to differences between a biosimilar's storage, handling, and route of administration and those of the reference product

2016 Trends in Biosimilars Report. Amgen website. http://www.amgenbiotech.com/resources/2016_Amgen_Trends_in_Biosimilars_Report_USA-BIO-122466.pdf. Published 2016. Accessed September 2018.

Supply Chain

Drug Shortage Considerations

- When available drug supplies are insufficient to meet medical needs, serious logistical, ethical and financial issues may occur and potentially lead to a variety of other health and safety issues
- Due to their highly specialized manufacturing process, sterile injectables make up a large percentage of these shortages
- Depending on how interchangeability/substitution issues are reconciled, biosimilars have the potential to lessen some of the burden of drug shortages

Ventola CL. *P T*. 2011;36:740-757.
FDA.gov. Preventing and mitigating drug shortages – FDA's and manufacturers' roles. http://www.fda.gov/downloads/Drugs/NewsEvents/UCM493617.pdf. Accessed September 2018.

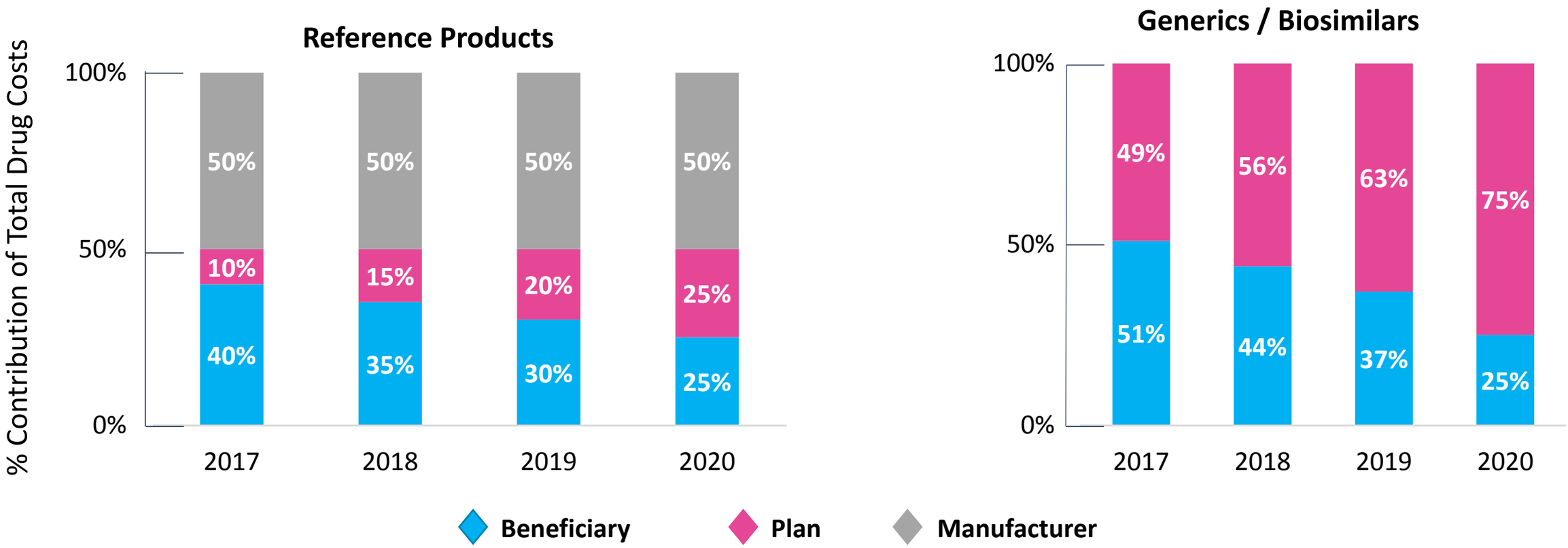
Financial Considerations: System

- Financial impact on the health care system
- Inpatient costs of administration
- Costs for patient and institutional support programs
- Medical information support
- Costs for technology changes
- Costs for pharmacovigilance
- Costs associated with drug shortages
- Outpatient margin
- Costs for monitoring the response to biosimilar treatment
- Potential additional monitoring costs when there is therapeutic interchange
- Influence of bundled contracting approaches on cost
- Influence of patient-assistance programs on cost
- Out-of-pocket costs for patients and potential impact on access and adherence

Ventola CL. *P T*. 2015;40:680–689.

Financial Considerations: Patient

Under Medicare Part D, biosimilars are being treated in a manner similar to generics since they are not subject to the 50% discount required for brand drugs when the Medicare Part D beneficiary is in the coverage gap



Closing the Donut Hole. Medicare Rights Center website. https://www.medicarerights.org/pdf/Closing-the-Donut-Hole-Chart.pdf. Published January 1, 2016. Accessed September 2018.

Education

"A clear understanding of the scientific principles of the biosimilar concept and access to unbiased information on licensed biosimilars are important for physicians to make informed and appropriate treatment choices for their patients."

"…patients will, at the very least, expect their HCPs [health care providers] to address their concerns that biosimilars are identical, and many may even want to review the data themselves."

Weise M, Bielsky MC, De smet K, et al. *Blood*. 2012;120(26):5111-7.
Rotenstein LS, Ran N, Shivers JP, Yarchoan M, Close KL. *Clin Diabetes*. 2012;30(4): 138-150.

Education: Physician Considerations

The feedback the FDA received on the January 2017 draft guidance included concerns from physicians regarding the extrapolation of indications, switching, labeling, naming, postmarketing studies, and the agency's engagement of disease experts when interchangeable products are reviewed for approval

- Recent experience with biosimilars shows that physicians will be reluctant to prescribe them and patients reticent to use them if:
  - They lack trust in the science behind the safety and interchangeability evidence required by regulators
  - The cost differences between the biosimilar and the reference listed product is too small

Syrop J. Physicians Express Concerns About Biosimilar Interchangeability to FDA. The Center for Biosimilars website. https://www.centerforbiosimilars.com/news/physicians-express-concerns-about-biosimilar-interchangeability-to-fda. Published June 30, 2017. Accessed September 2018.

Education: Patient Considerations

- Poor adherence to a prescription is a well-known issue affecting health care and a leading cause of preventable morbidity, mortality, and cost in chronically ill patients
- Patient support programs are critically important for some patients and can influence physician behavior or serve as a point of differentiation between biosimilars
- Biosimilar manufacturers should build comparable support programs to those available with reference biologics
  - Likewise, payers and SPPs are responsible for dissemination of said programs to applicable patients and for creating similar educational and support programs for biosimilars

Adherence to long-term therapies. World Health Organization website. http://www.who.int/chp/knowledge/publications/adherence_full_report.pdf?ua=1. Published 2003. Accessed September 2018
2016 Trends in Biosimilars Report. Amgen website. http://www.amgenbiotech.com/resources/2016_Amgen_Trends_in_Biosimilars_Report_USA-BIO-122466.pdf. Published 2016. Accessed September 2018.

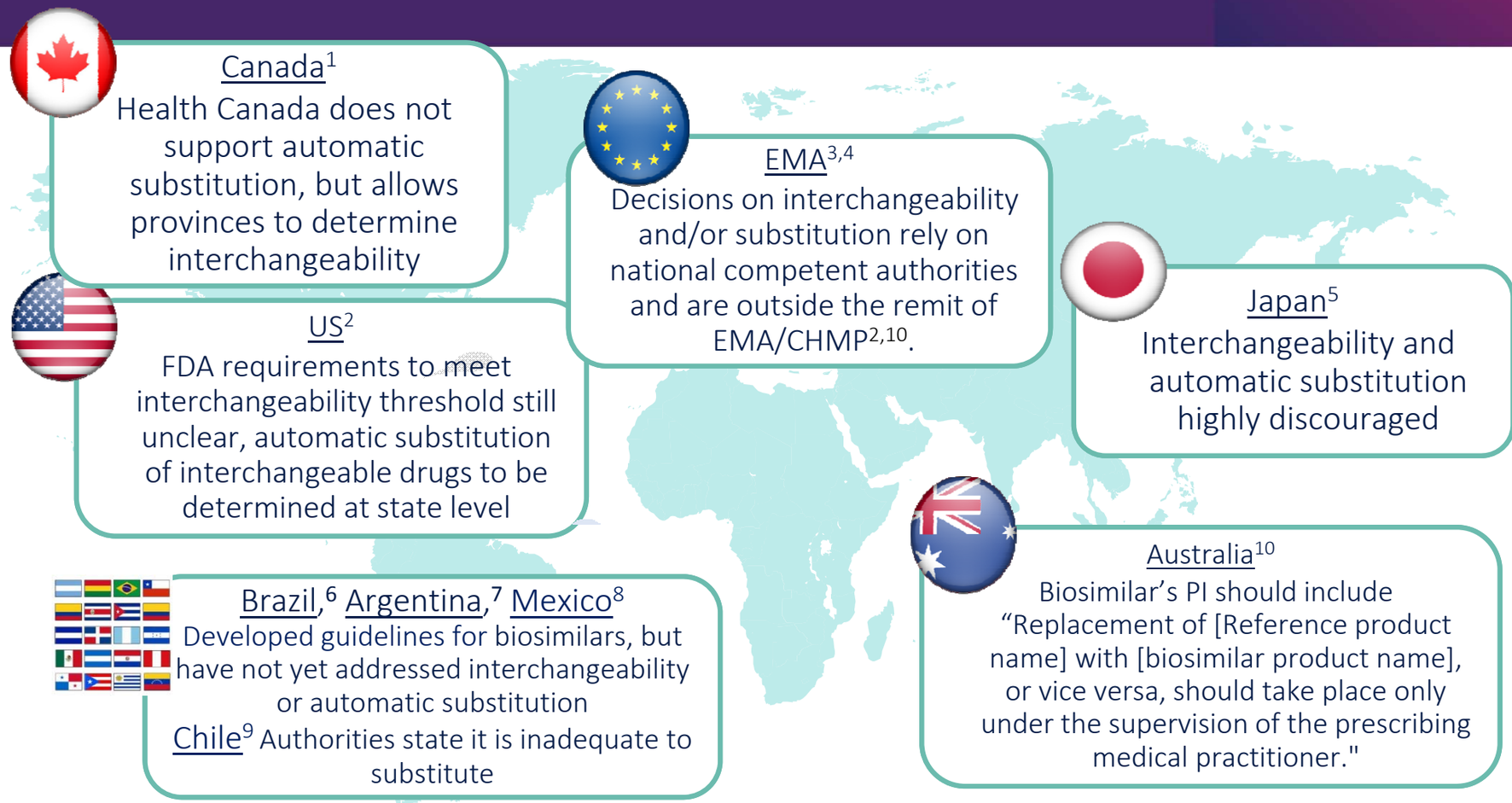
Summary

- Biosimilars offer the potential to at least partially mitigate the rising specialty drug trend
- However, this potential is tempered by challenges related to modest uptake by providers, interchangeability/substitution concerns, and operational challenges for payers
- Recognizing the differences between biosimilars and reference biologics, payers should be prepared to manage these challenges by having specific biosimilar protocols and information systems in place

Therapeutic Scenarios for Biosimilar Substitution

Vanita K. Pindolia, PharmD, BCPS, MBA
Vice President, Ambulatory Clinical Pharmacy Programs_PCM
Henry Ford Health System/Health Alliance Plan of Michigan

Interchangeability and Substitution



Canada[1]
Health Canada does not support automatic substitution, but allows provinces to determine interchangeability

EMA[3,4]
Decisions on interchangeability and/or substitution rely on national competent authorities and are outside the remit of EMA/CHMP[2,10].

US[2]
FDA requirements to meet interchangeability threshold still unclear, automatic substitution of interchangeable drugs to be determined at state level

Japan[5]
Interchangeability and automatic substitution highly discouraged

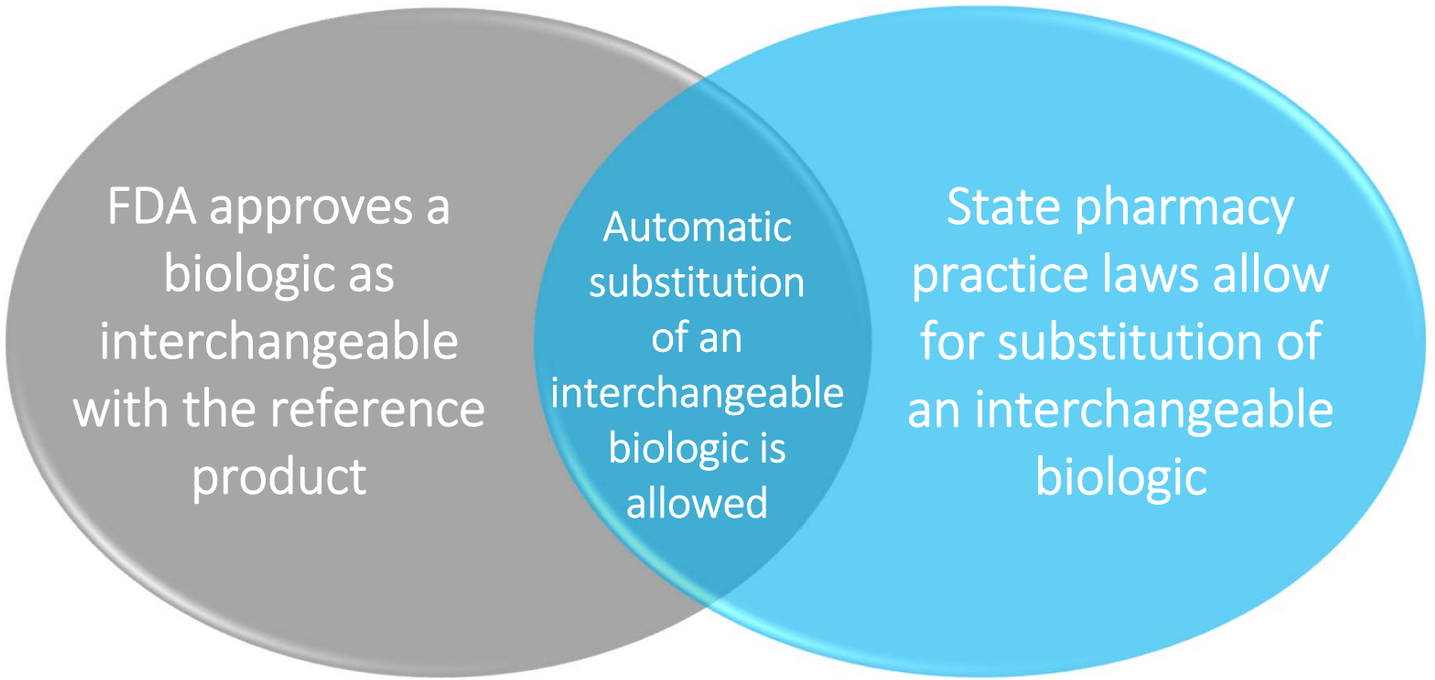
Australia[10]
Biosimilar's PI should include "Replacement of [Reference product name] with [biosimilar product name], or vice versa, should take place only under the supervision of the prescribing medical practitioner."

Brazil,[6] **Argentina**,[7] **Mexico**[8]
Developed guidelines for biosimilars, but have not yet addressed interchangeability or automatic substitution

Chile[9] Authorities state it is inadequate to substitute

1. Health Canada Interchangeability and Substitutability of Subsequent Entry Biologics, July 20; www.hc-sc.gc.ca/dhp-mps/ brgtherap/applic-demande/guides/seb-pbu/01-2010-seb-pbu-qa-qr-eng.php#q15. Accessed April 2017. 2. FDA Biosimilar Guidance Webinar, February 15, 2012; 3. EMA, Questions and Answers on biosimilar meds; 4. European Commission: What you need to know about biosimilar medicinal products. Consensus Information Paper 2013. 5. MHLW Guideline for Ensuring Quality, Safety and Efficacy of Biosimilar Products, March 2009; 6. ANVISA: Resolucao RDC N° 55, de 16 de Deem bro de 2010; Diario Oficial da Uniao-Secao 1; N° 241; 7. ANMAT, Disposición N° 7729/2011 (publicado el 21 de Noviembre de 2011); 6. Proyecto de PROY-NOM-257-SSA1 -2013; 8. Norma Técnica Nº 170 Sobre Registro Sanitario de Productos Biotecnológicos Derivados de Técnicas ADN Recombinantes; 9. Diario Oficial de la República de Chile, 6 de Septiembre de 2014) 10. TGA Biosimilar Guidance; 30 July 2013;

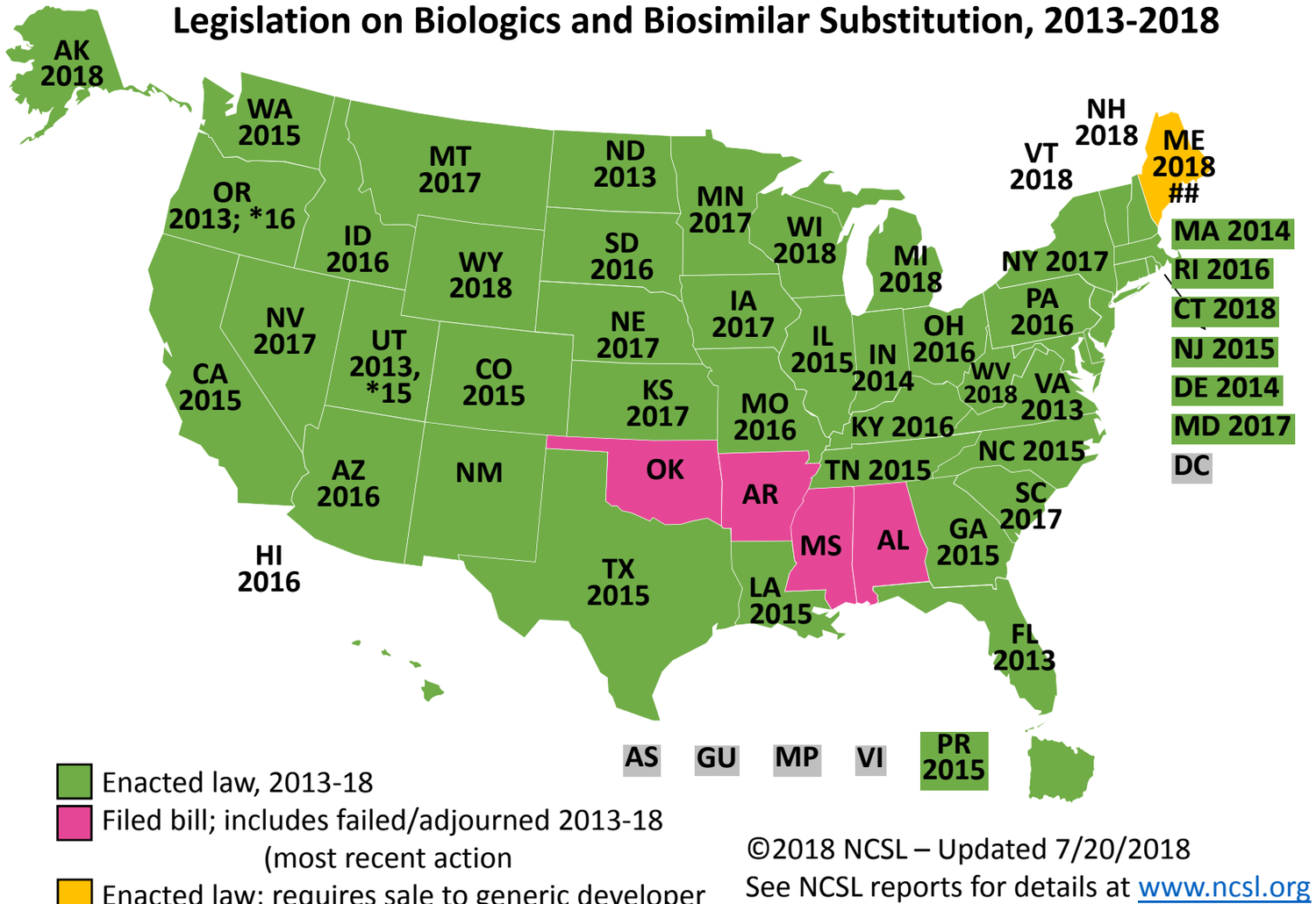
State Regulations Govern Automatic Substitution of an Interchangeable Biologic



- Pharmacists will need to track interchangeable biologics and may need to notify the physician if an automatic substitution occurs to ensure accurate medical records
- It is not yet known if interchangeability may be granted for all or only a subset of indications

National Conference of State Legislatures. www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars. Accessed April 2017.

Status of State Legislation on Automatic Substitution[1,2]



See NCSL reports for details at www.ncsl.org

- Automatic substitution is defined as a pharmacist providing a different product than that prescribed, without consulting the prescriber prior to dispensing

Potential criteria for pharmacy-level substitution of biologics

1. Designation as interchangeable by FDA
2. Doctor may specify "dispense as written"
3. Pharmacist informs prescriber of product dispensed
4. Patient notification/consent
5. Pharmacy retains record of product dispensed

www.ncsl.org/research/health/state-laws-and-legislation-related-to-biologic-medications-and-substitution-of-biosimilars. Accessed September 2018.

Provider Reluctance was Prevalent with Respect to Switching Patients to Biosimilars

A 2016 survey of specialty physicians found that these clinicians were more comfortable limiting biosimilars to their treatment-naïve patients rather than switching stable patients from a biologic to a biosimilar

A reluctance to switch stable patients to a biosimilar was also identified in a separate 2016 study; only 1 of 8 rheumatologists surveyed said that they would switch a stable patient from a reference product to a biosimilar

Biosimilars in the US healthcare system: physician and access decision maker perspectives in 2016. http://www.precisionforvalue.com/wpcontent/uploads/2016/11/Precision_Biosimilar_Trend_Report_Sneak_Preview.pdf.
InCrowd. MicroSyndicated Study: Biosimilar Perceptions & Expectations. Published February 10, 2016.

Biosimilars Ability to Lower Cost of Care: Great Impact on Provider's Acceptance for Biosimilar

As reference biologics are starting to lose patent protection, single biosimilar products are entering the market

- Typically cost neutral to reference product (post-rebates) at product launch (approx. 20% lower than base price of reference product)
- Recent launch of Biosimilar Pegfilgrastim has changed that paradigm with > 30% price decrease over Neulasta

Entry of multiple biosimilars for a reference biologic used in provider setting

- Difference in price over time with ASP vs AWP
- As providers purchase drug and true price is known, ASP continues to decrease
- AWP remains higher
- Hospitals/health systems formulary drug of choice are biosimilars

Quarter	Remicade[1] (J1745)	Biosimilar (Q5102)		Biosimilar vs. Innovator
		Inflectra[2]	Renflixis[3]	
2017: Q1	$82.22	$100.31	n.a.	+22%
Q2	$85.59	$100.31	n.a.	+17%
Q3	$85.47	$80.19	n.a.	-6%
Q4	$87.15	$78.72		-10%

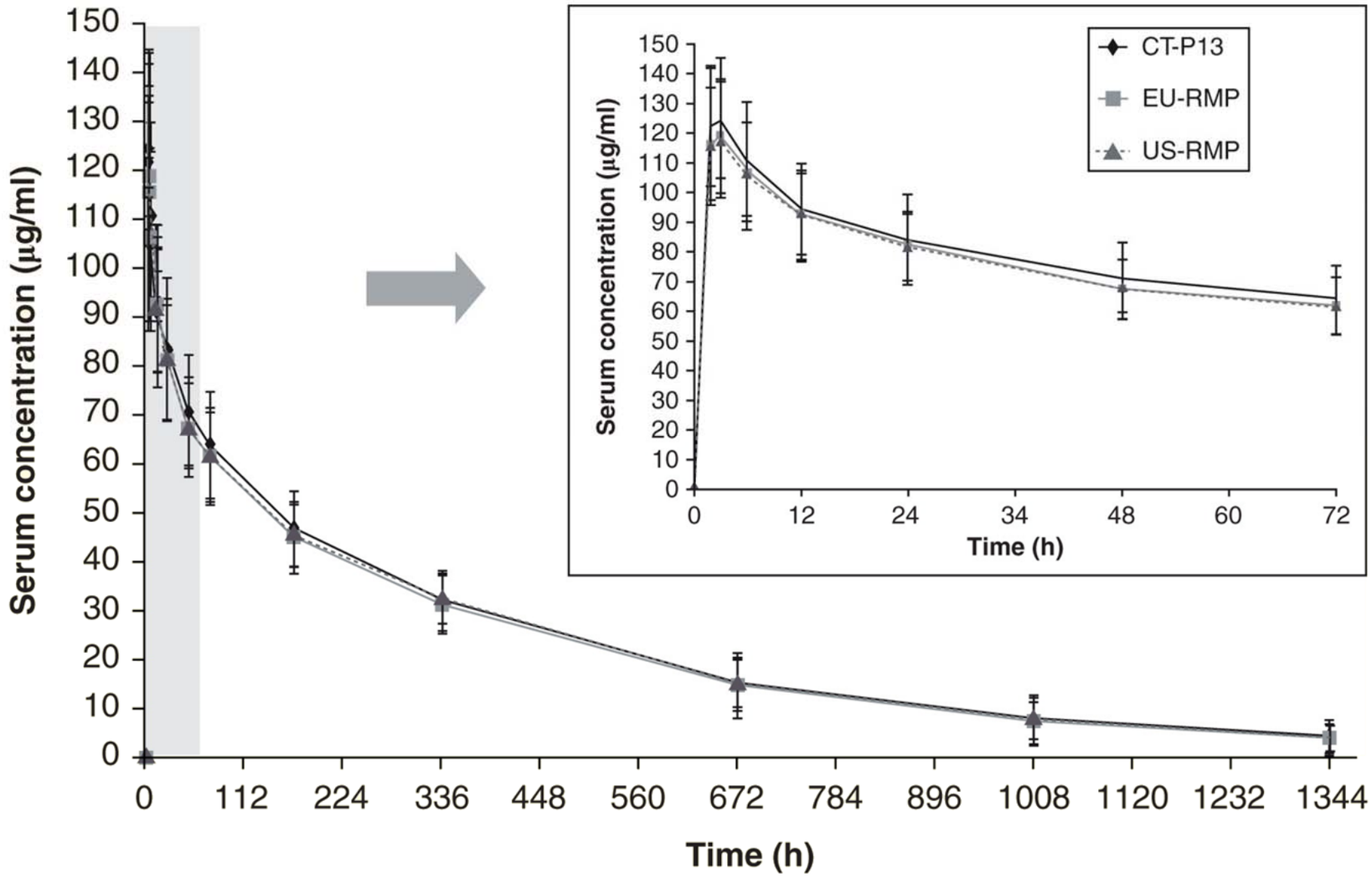
Other Factors

- Risk-based contracting
- Payer step-care policies

Remicade's payment rate is based on the product's Average Sales Price (ASP) plus 6%.; 2. Inflectra's payment rate for 2017:Q1 and 2017:Q2 was based on the product's Wholesale Acquisition Cost (WAC) plus 6%. Inflectra's payment rate for 2017:Q3 onward is based on the product's ASP plus 6% of Remicade's ASP.; 3. Renflexis' payment rate for 2017:Q4 is based on the ASP for the consolidated billing code Q5102, which was computed using Inflectra sales in the second quarter of 2017. Source: Pembroke Consulting analysis of Centers for Medicare & Medicaid Services (CMS) data

Pharmacokinetic Findings Pertaining to Biosimilars Are Compelling for Providers and Payer Stakeholders

CT-P13=Biosimilar infliximab; EU-RMP=Europe-approved reference medicinal product; US-RMP=US-licensed reference medicinal product



Park W, et al. *Exp Rev Clin Immunol*. 2015;11(supl1):25-3

Additional Data Pertaining to Real-World Efficacy (RWE) and Switching Patterns are Necessary

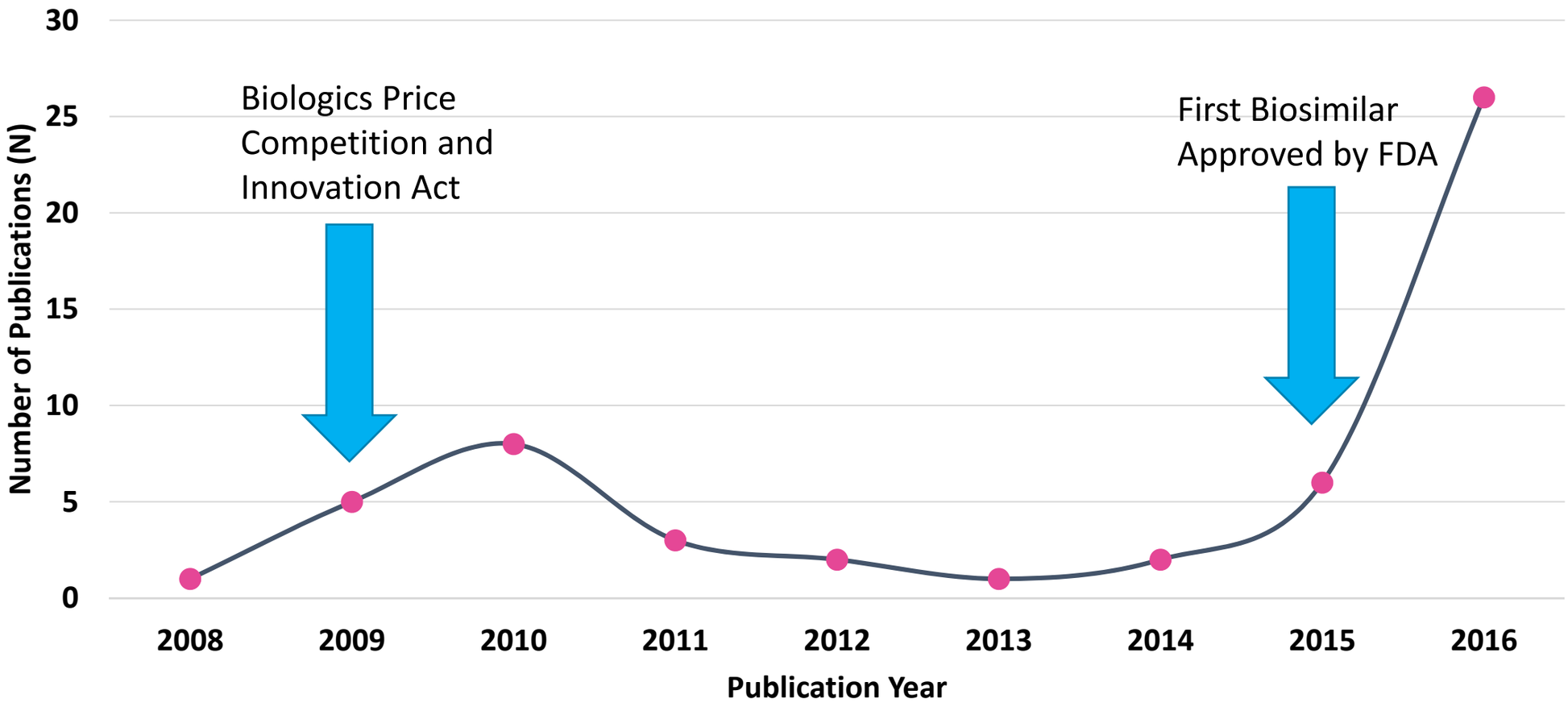
Physicians have asserted that clinical trial data could improve their understanding of biosimilars and help them integrate biosimilars into their practices

Survey data support further physician education initiatives that outline the differences between biosimilars and reference biologics

Physicians desire additional safety and real-world RWE data for biosimilars, as well as further research into treatment switching patterns

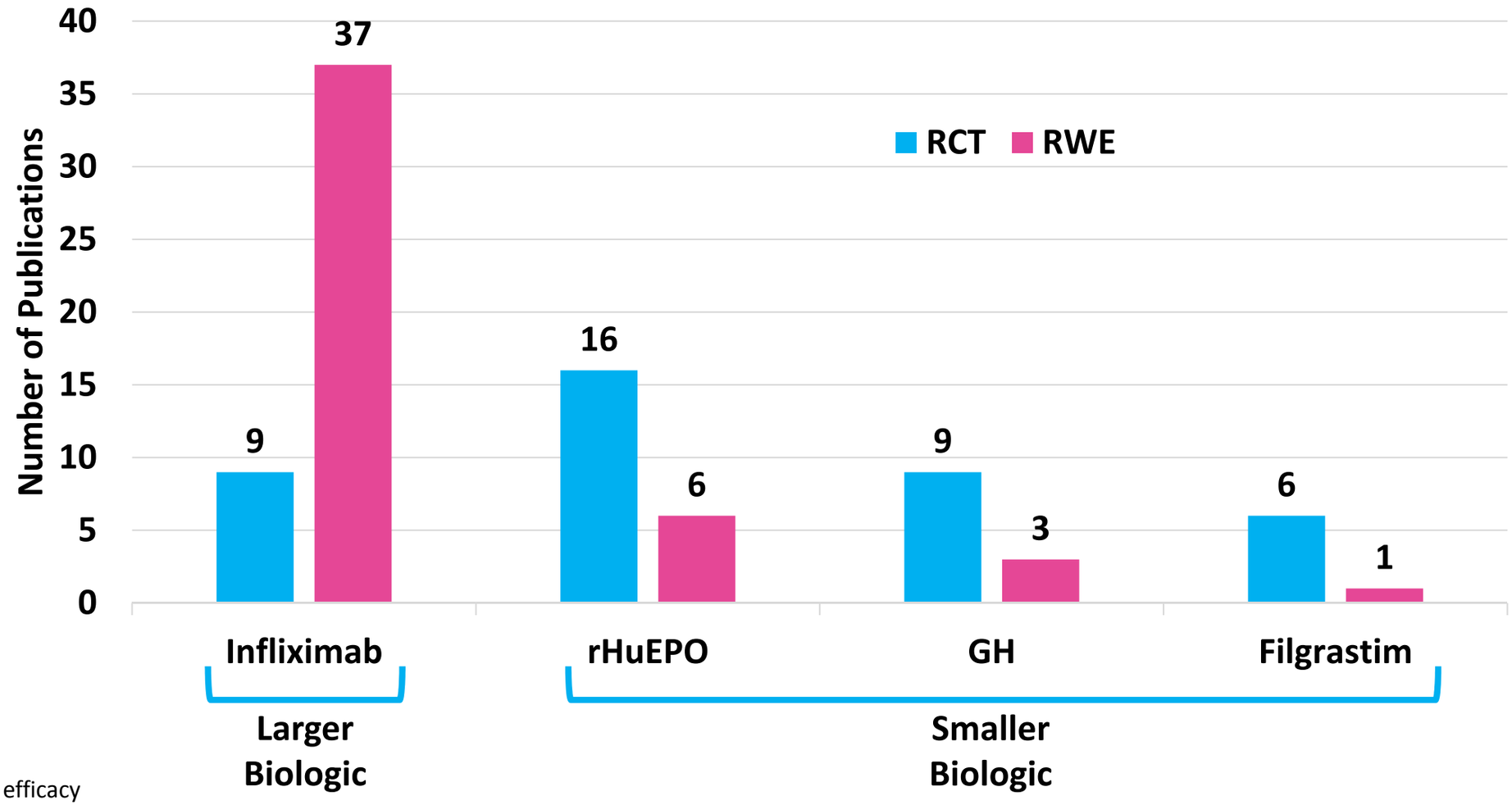
Woollett G. http://avalere.com/expertise/life-sciences/insights/use-ofstep-through-policies-for-competitive-biologics-among-commercial-us.

The Body of Literature Pertaining to Reference Biologic/ Biosimilar Switching Has Grown Exponentially in Recent Years



Cohen HP, et al. *Drugs*. 2018;78:463-478.

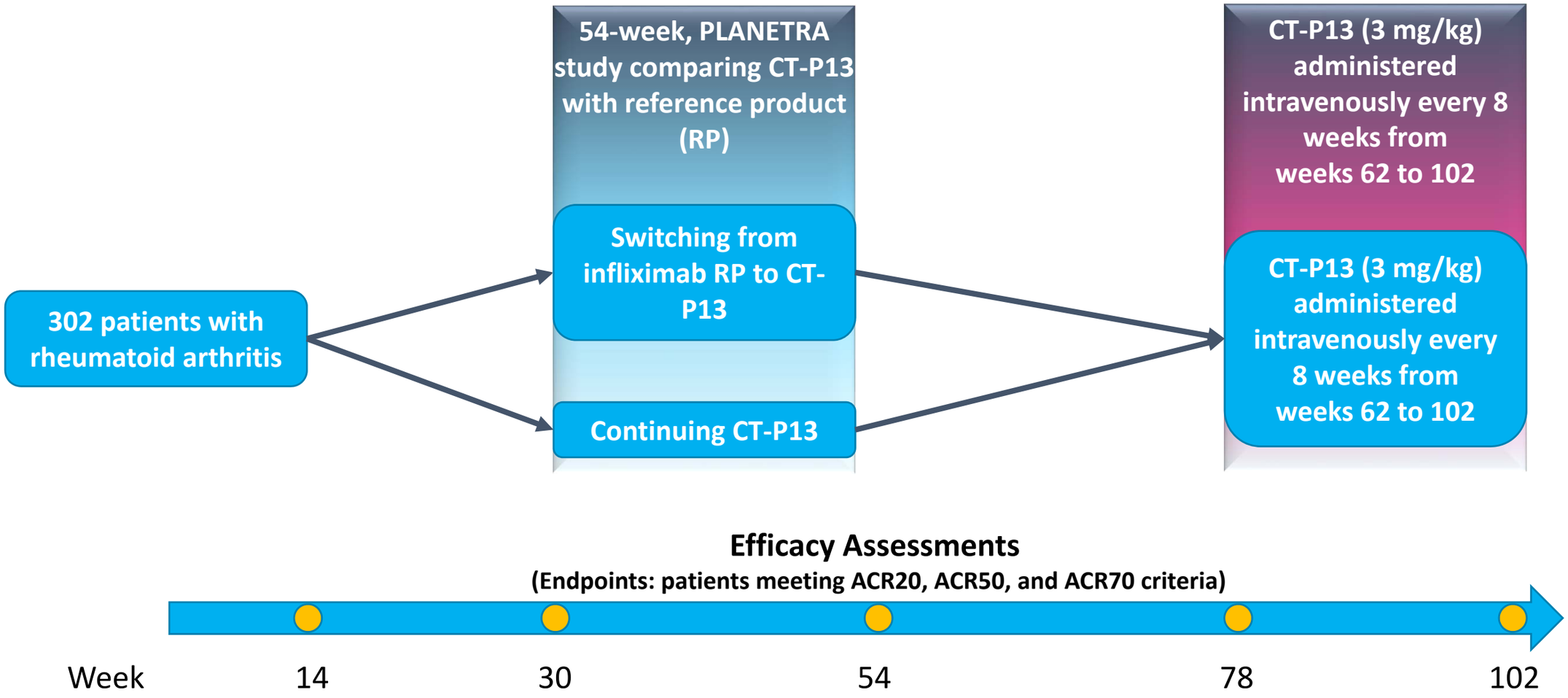
Real-World Efficacy (RWE) Studies Have Become More Prevalent than RCTs for Larger Molecule Biosimilars



RWE=Real-world efficacy
RCTs=Randomized, controlled trials

Cohen HP, et al. *Drugs*. 2018;78:463-478.

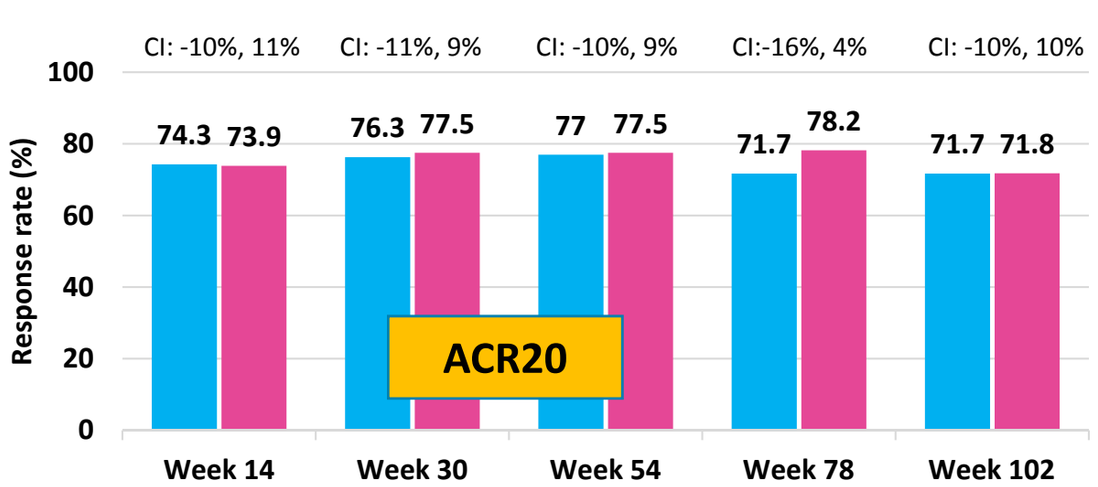
Biosimilar Infliximab in RA: Trial Design and Methods

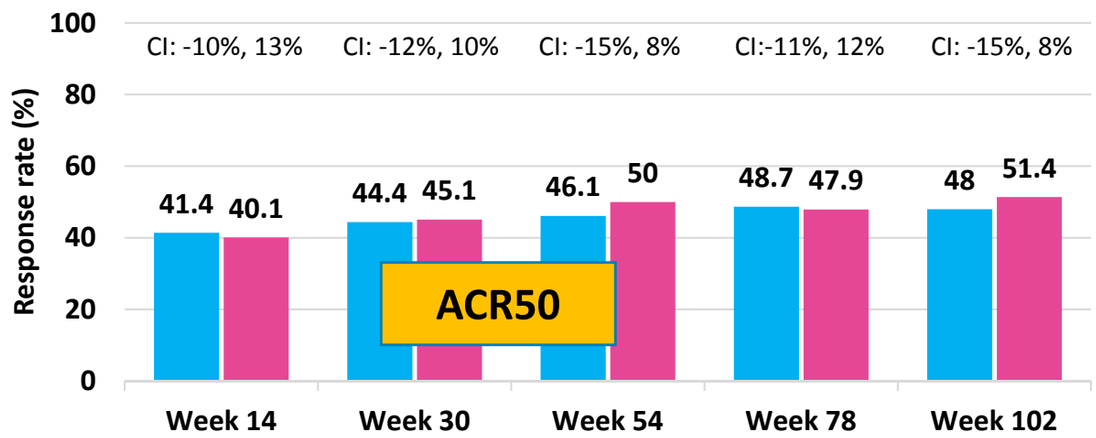


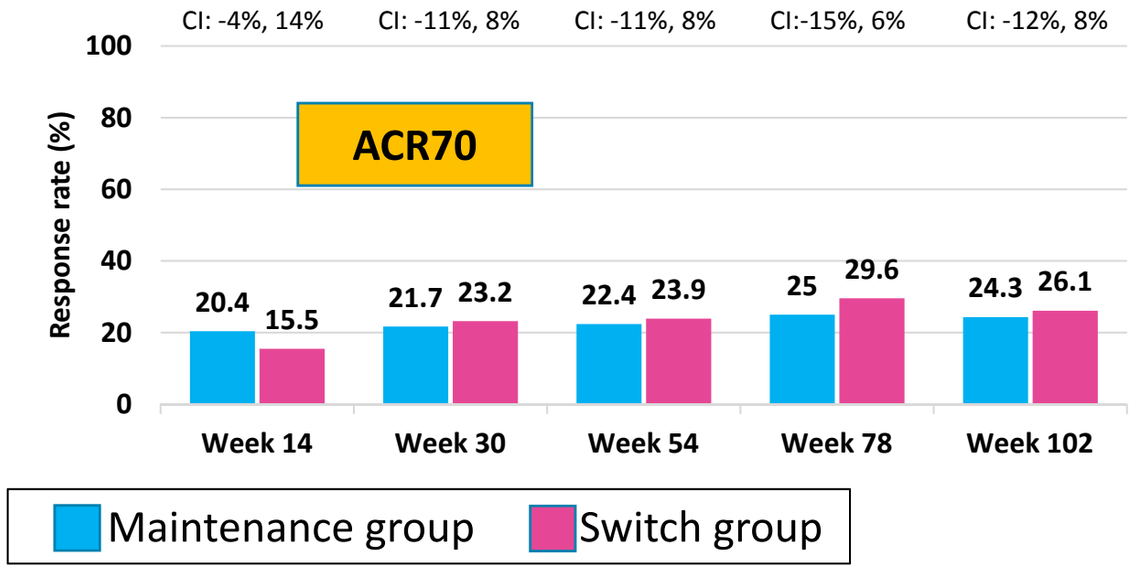
RP, reference product; RA, rheumatoid arthritis; ACR, American College of Rheumatology.

Yoo, DH et al. *Ann Rheum Dis.* 2017;76(2):355–363.

Biosimilar Infliximab in RA: Key Findings







- Patients with RA received methotrexate, switched from RP to CT-P13 were not associated with any detrimental effects on efficacy, immunogenicity or safety
- CT-P13 remained efficacious and was well tolerated during a 2-year treatment period

RA, rheumatoid arthritis; RP, reference product.

Yoo, DH et al. *Ann Rheum Dis.* 2017;76(2):355–363.

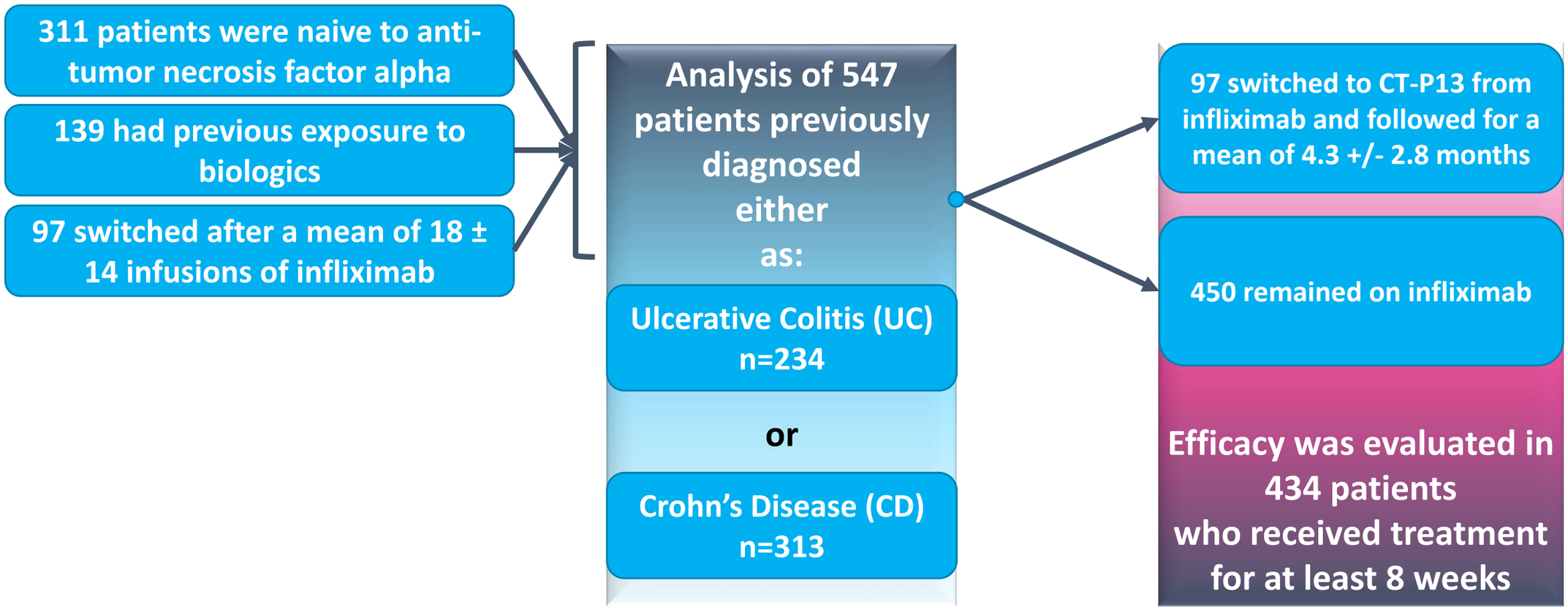
Biosimilar Infliximab in RA: Conclusions

- Data support long-term efficacy of CT-P13 in patients with RA
- Data show CT-P13 biosimilar of infliximab does not have any unusual immunogenicity
- This study provides confidence that biosimilar infliximab is appropriate for use in patients who are currently doing well on reference infliximab

RA, rheumatoid arthritis; RP, reference product.

Yoo, DH et al. *Ann Rheum Dis.* 2017;76(2):355–363.

Biosimilar Infliximab in UC: Trial Design and Methods



Fiorino G, et al. *Inflamm Bowel Dis.* 2017;23(2):233–243.

Biosimilar Infliximab in UC: Key Findings

- Efficacy in terms of induction and/or maintaining of remission/response was high

Patient Type	8 weeks	16 weeks	24 weeks
Naive	95.7%	86.4%	73.7%
Pre-exposed	97.2%	85.2%	62.2%
Switched	94.5%	90.8%	78.9%

- Preliminary data on efficacy and safety of CT-P13 were in line with those of infliximab.

Fiorino G, et al. *Inflamm Bowel Dis.* 2017;23(2):233–243.

Biosimilar Infliximab in UC: Conclusions

- Given this similarity of biosimilars to reference products, we should expect biosimilars to perform similarly with similar outcomes
- This and similar studies may make doctors and patients more comfortable with the idea of using a biosimilar
- Insurers may use these data to encourage greater use of biosimilars if doing so provides cost savings

Fiorino G, et al. *Inflamm Bowel Dis.* 2017;23(2):233–243.

Impact of Biosimilars on Reducing Total Cost of Care for Autoimmune/Inflammatory Conditions

- Newly identified patients versus Active conversion is more likely in chronic conditions such as RA, UC, etc.
- Data from switching studies show maintenance of efficacy and tolerability with minimal immunogenicity

Quarter	Remicade[1] (J1745)	Biosimilar (Q5102)		Biosimilar vs. Innovator
		Inflectra[2]	Renflixis[3]	
2016: Q3	$82.28	n.a.	n.a.	n.a.
Q4	$82.87	n.a.	n.a.	n.a.
2017: Q1	$82.22	$100.31	n.a.	+22%
Q2	$85.59	$100.31	n.a.	+17%
Q3	$85.47	$80.19	n.a.	-6%
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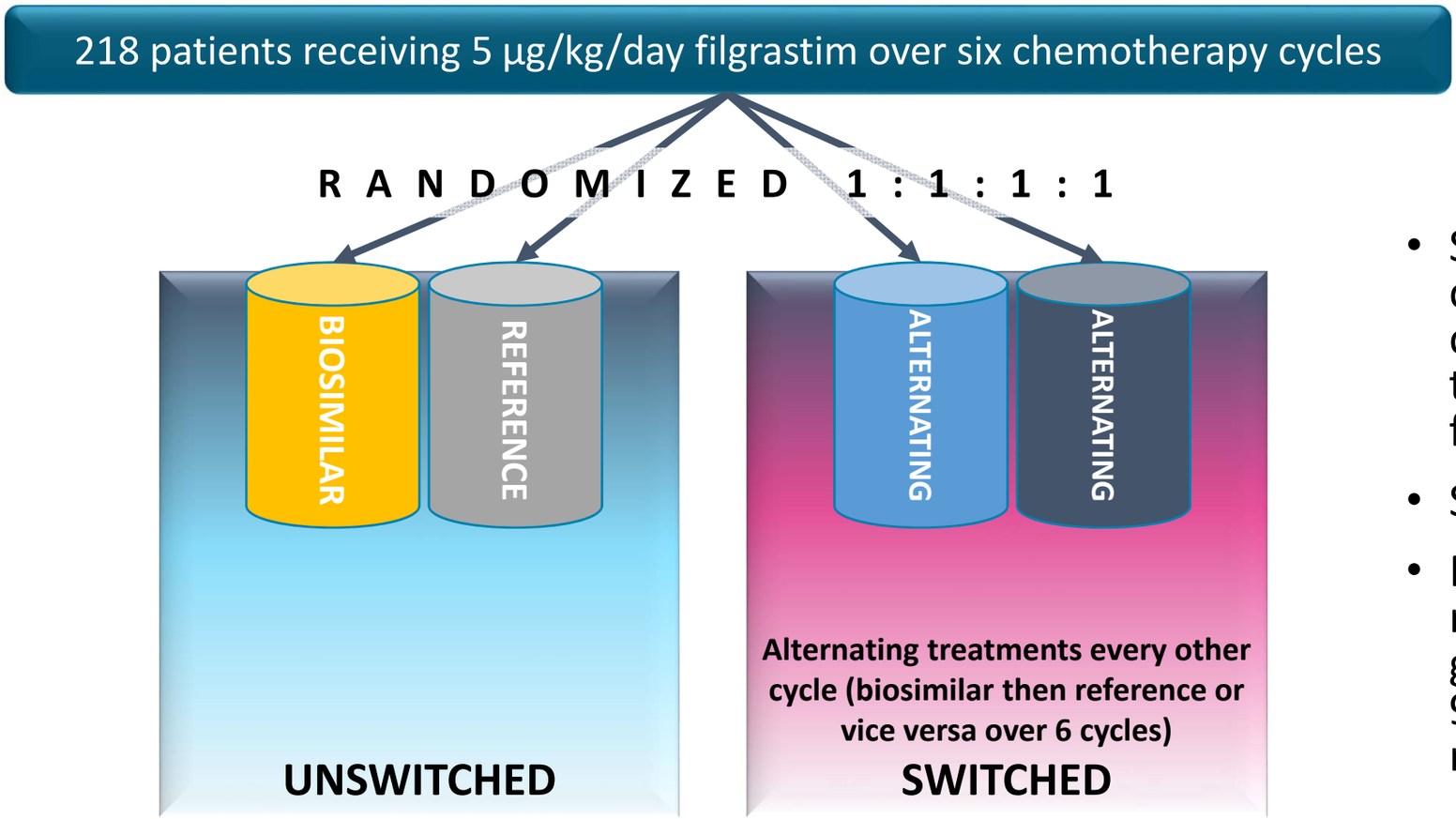
3. Renflexis' payment rate for 2017:Q4 is based on the ASP for the consolidated billing code Q5102, which was computed using Inflectra sales in the second quarter of 2017.

Source: Pembroke Consulting analysis of Centers for Medicare & Medicaid Services (CMS) data

Biosimilar GSCF: Trial Design and Methods



- Since the switch occurred from cycle 2 onwards, this analysis compared pooled switched groups to the unswitched reference group for efficacy during cycles 2-6.
- Safety assessed
- Non-inferiority in febrile neutropenia (FN) rates between groups for cycles 2-6 was shown if 95% were within a pre-defined margin of - 15%

Blackwell K, et al. *Ann Oncol*. 2018;29(1):244-249.

Biosimiliar GCSF: Key Findings

The incidence of FN was 0% (reference) versus 3.4% (n = 3, switched) across cycles 2-6, with a difference of - 3.4% (95% confidence interval: -9.65% to 4.96%), showing non-inferiority

Infections occurred in 9.3% (switched) versus 9.9% (reference)

No neutralizing antibodies were detected

There were no clinically meaningful differences regarding efficacy, safety or immunogenicity when switching from reference to biosimilar GCSF, or vice versa

Blackwell K, et al. *Ann Oncol*. 2018;29(1):244-249.

Therapeutic Scenario: Biosimilars in Oncology Supportive Care

Data from trials show similar efficacy and tolerability to reference agents, even in switching scenarios, with little difference in outcomes

Active conversion may require hematologists/oncologists more time to feel comfortable with switching mid-chemo cycle for high risk populations.

Case by case switches will allow physicians/extendors to gain more experience necessary to increase comfort level for mid-cycle switches.

Influencing the Uptake of Biosimilars in Managed Care Pharmacy

- Engage various stakeholders:
  - Educate patients as decision-makers and stewards of their own health care dollars
  - Educate physician specialties regarding comparable clinical outcomes and safety
  - Share data pertaining to switching and outcomes with employers and other health care purchasers
  - Share cost differences, especially over time, as ASP of biosimilars decline (health system providers interested with a growing number of risk-based contracts)
- Promote active and regular dialogue with the above groups of stakeholders, particularly fully insured employers, and emphasize member satisfaction in these discussions
- Work with stakeholders on active conversion of members/patients prescribed reference biologics; minimal savings are generated via addressing new starts alone
- Incorporate a two-tiered specialty benefit with lower OOP costs for biosimilars