

IBD

and Biosimilars

What Health Care Providers Need to Know

November 6, 2020



Program Sponsor

Thank you to



Program Funders

This program is supported by independent medical education grants from:

AMGEN



**Boehringer
Ingelheim**

Learning Objectives

Section 1: The Biosimilar Development Process

- Understand the biosimilar development process
- Discuss the Biosimilars Price Competition and Innovation Act (BPCIA)
- Review FDA definitions (nomenclature) and distinction between biosimilars, biologics, small molecules, and generics
- Understand the regulatory requisites associated with biosimilars including PK/PD, extrapolation, interchangeability and pharmacovigilance

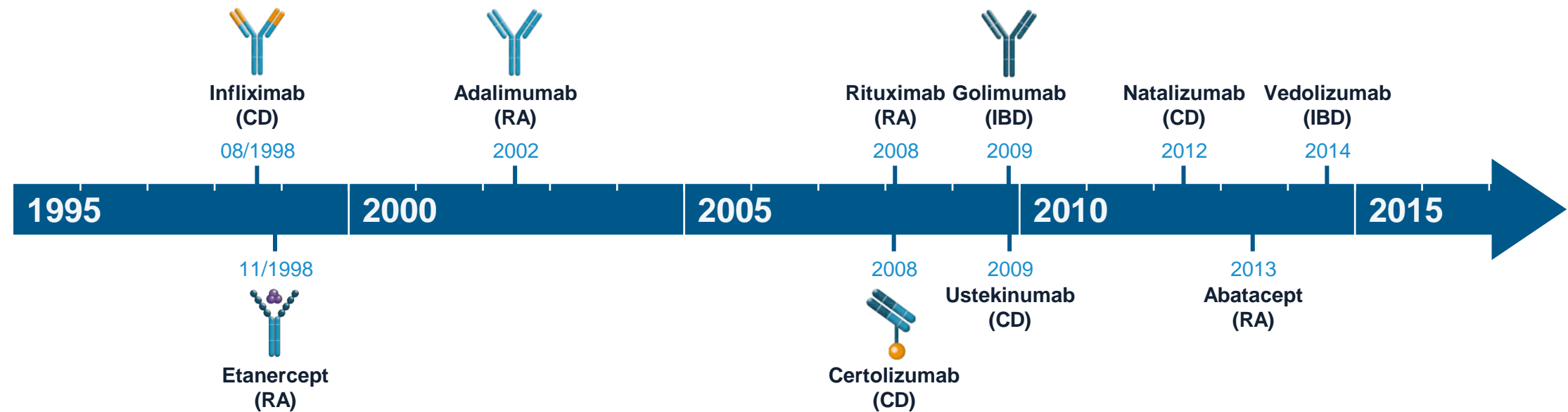
The Biosimilar Development Process

Section 1

Biological products have revolutionized treatment of autoimmune and inflammatory disorders

For nearly 20 years, biological products have become a cornerstone in the treatment of RA, Pso, PsA, AS, JIA, and IBD, revolutionizing the therapeutic approach and treatment paradigms ^{1, 2}

US dates and indications of initial approvals for anti-TNF biological products ^{3–14}



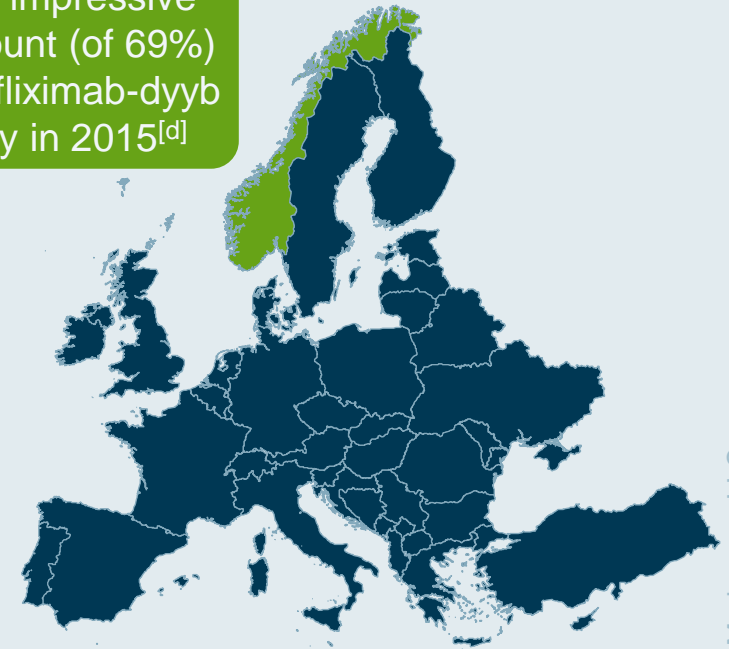
1. Blüml S *et al.* *Int Immunol* 2012;24:275–281. 2. Ackerman C *et al.* *Expert Opin Ther Targets* 2007;11:1369–1384. 3. Pederson J *et al.* *World J Gastroenterol* 2014;20:64–77. 4. US FDA. Etanercept product approval information. Accessed May 2015. 5. US FDA. Infliximab product approval information. Accessed May 2015. 6. US FDA. Adalimumab product approval information. Accessed May 2015. 7. MedPage Today. FDA Approves Rituxan for Refractory Rheumatoid Arthritis. March 1, 2006. 8. US FDA. News Release. Accessed May 2015. 9. Johnson and Johnson. Press Release. Accessed May 2015. 10. US FDA. Golimumab label. Accessed June 3, 2020. 11. US FDA. Ustekinumab label. Accessed June 3, 2020. 12. US FDA. Natalizumab label. Accessed June 3, 2020. 13. US FDA. Abatacept label. Accessed June 3, 2020. 14. US FDA. Vedolizumab label. Accessed June 3, 2020.

Growth and success of anti-TNF biologics has come at a cost

- While <2% of Americans use biologics, they represent ~40% of all prescription drug spending^[a]
 - For outpatient IBD medications, the average biologic-taking patient accounted for \$36,051 per member per year in 2015^[b]
- Biologics cost an estimated \$2.6 billion to develop^{*[c]}
- A recently published Rand Corporation analysis estimated that, from 2017 to 2026, biosimilars have the potential to reduce direct spending on biologic therapies by \$54 billion^[a]

Price reductions varied considerably between the European countries

The most impressive price discount (of 69%) seen for infliximab-dyyb in Norway in 2015^[d]



© Medscape, LLC

*Includes approximate average out-of-pocket costs of \$1.4 billion and time costs of \$1.2 billion.

a. Mulcahy AW, et al. Rand Health Q. 2018;7:3; b. Yu H, et al. Aliment Pharmacol Ther. 2018;47:364-370; c. DiMasi JA, et al. J Health Econ. 2016;47:20-33; d. Burri E, et al. Swiss Med Wkly. 2019;149:w20148.

Legislation to drive cost savings is the biggest factor driving biosimilar development

Global socioeconomic

- Mounting cost pressures on government budgets
- Desire to increase access to patients

Regulatory initiatives

- EMA in 2006
- FDA 2009: Biologics Price Competition and Innovation Act—BPCIA
 - To create an abbreviated licensure pathway for biological products that are demonstrated to be “biosimilar” to or “interchangeable” with an FDA-licensed biological product.
- Canada, Japan, Korea

Other factors

- Expiration of patents
- Technological innovation in biomanufacturing
 - Better selection of high-producing cell lines
 - Less costly bioreactors
 - Improved production yields, time and lower costs

Potential cost savings could increase access to care

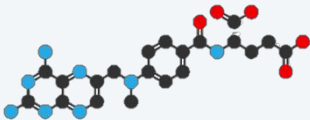

3.1% of total biologic sales in 2016

- range 0.2- 10.5%; or \$3.3 Billion of 2016 total sales

\$54 billion cost saving potential of biosimilars over 10 years

- Sensitivity analyses suggest a range of \$25 to \$150 billion
 - Varying biosimilar penetration (5% to 60%; mean 28%)

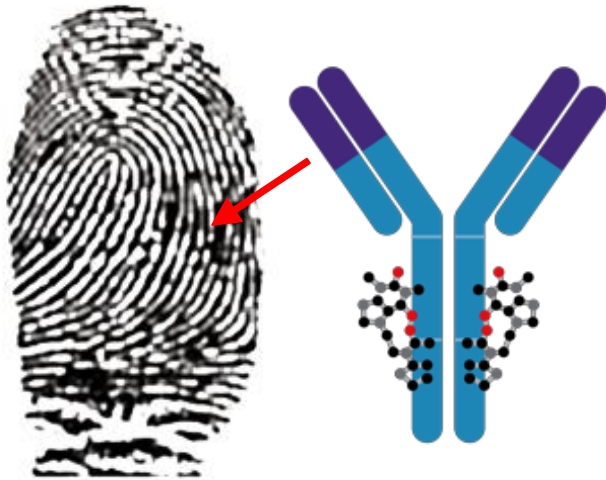
Biological products are complex, with distinct differences compared with conventional ("small molecule" medicines)

Small Molecules	Properties	Biological Products (Protein-based Drugs)
<p>Methotrexate MW=454 Da</p>  <p>Simple² and well defined³</p>	<p>Example of Molecule Structure and Size</p>	<p>Monoclonal antibody MW≈150,000 Da</p>  <p>Complex, with many options for post-translational modification⁵</p>
<p>Replicable in different laboratories</p>	<p>Manufacturing</p>	<p>Each manufactured in a unique living cell line</p>
<p>Relatively stable; usually degrades with first-order kinetics</p>	<p>Stability</p>	<p>Sensitive to storage and handling conditions</p>
<p>Reactions are intrinsic to the patient and not easily attributable to product</p>	<p>Immunogenicity</p>	<p>Reactions may be attributable to both product- and host-related factors</p>

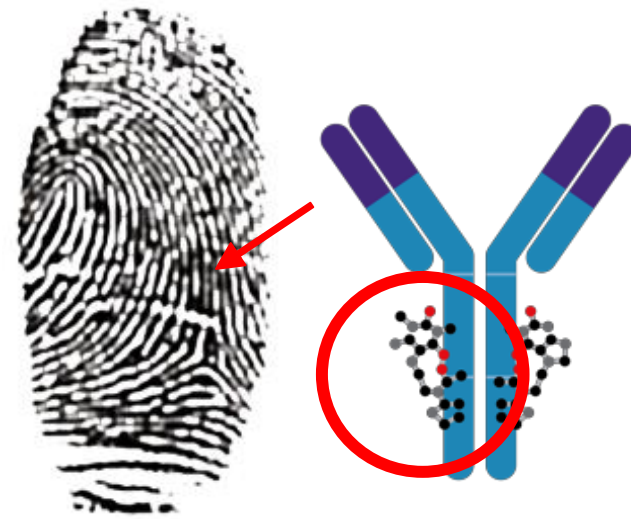
Biosimilars are similar to originator biological products

Like fingerprints from identical twins, biosimilars are similar to originator biological products but not identical,¹ though they are tested for equivalent structure and function².

Originator Biological Product



Biosimilar



Biosimilars are defined as having equivalent efficacy and safety to originator biological products

Food and Drug Administration (US FDA)

“Highly similar to reference product notwithstanding minor differences in clinically inactive components [with] **no clinically meaningful differences** between the biosimilar and the reference product...”¹

European Medicines Agency (EMA)

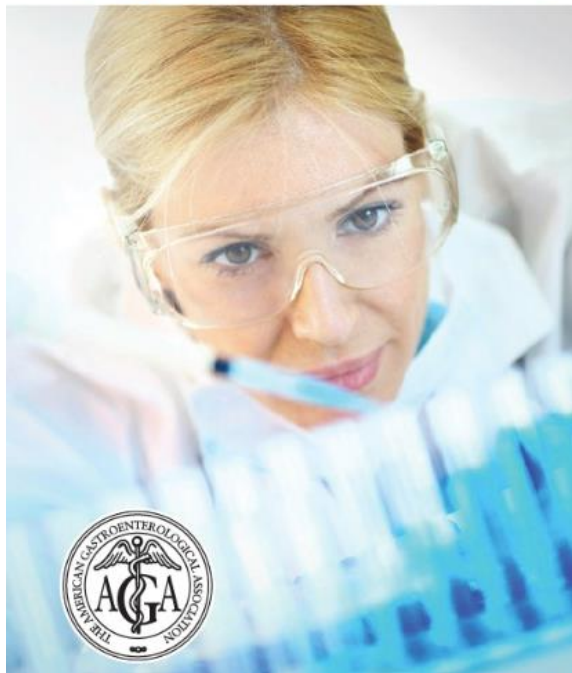
“Essentially the same biological substance, though there may be minor differences due to their complex nature and production methods...[differences] will **have been shown not to affect safety or effectiveness**”²

World Health Organization (WHO)

“...**Similar in terms of quality, safety, and efficacy** to an already licensed reference biotherapeutic product”³

Biosimilars \neq Generics

PHYSICIANS' POCKET GUIDE TO
**Understanding
 Biologics and Biosimilars**



	Generics	Biosimilars
Size	Small	Large
Structure	Simple, well-defined	Complex (made up of many ingredients that are not well-defined)
Manufacturing	Predictable chemical process; exact copy can be made	Each manufactured in a unique living cell; similar, but not exact, copy can be made
Stability	Relatively stable	Highly sensitive to changes in environment (manufacturing and handling conditions)
Development cycle	Takes about 3 years to develop	Takes about 7 to 8 years to develop
Quality Assurance	About 50 QA tests done before possible approval	About 250 QA tests done before possible approval

Biosimilars: FDA definitions and requirements

A biological product that is **HIGHLY similar** to the reference product notwithstanding **minor** differences in **clinically inactive** components.

No **clinically meaningful difference** between the biological product and the reference product in terms of **safety, purity, and potency**.



Large and generally complex molecules



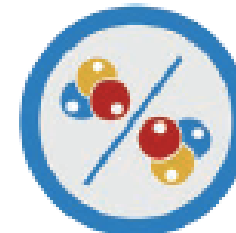
Produced from living organisms



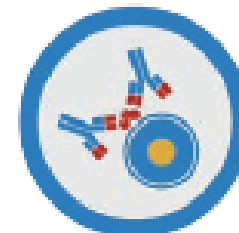
Carefully monitored to ensure consistent quality



Purity



Molecular structure

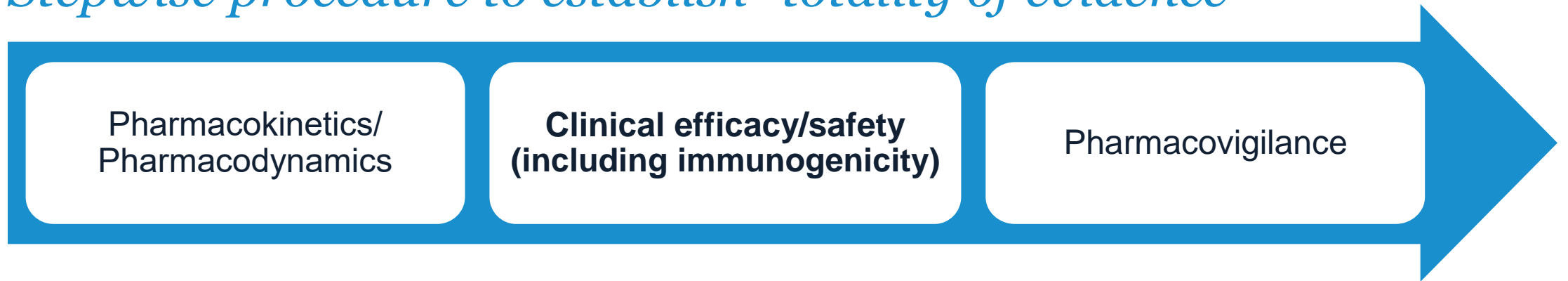


Bioactivity

The data from these comparisons must show that the biosimilar is highly similar to the reference product.

General principles to demonstrate biosimilarity: “Totality of Evidence” is evaluated

Stepwise procedure to establish “totality of evidence”^{1,2}



Pharmacokinetic
and, if needed,
pharmacodynamic studies

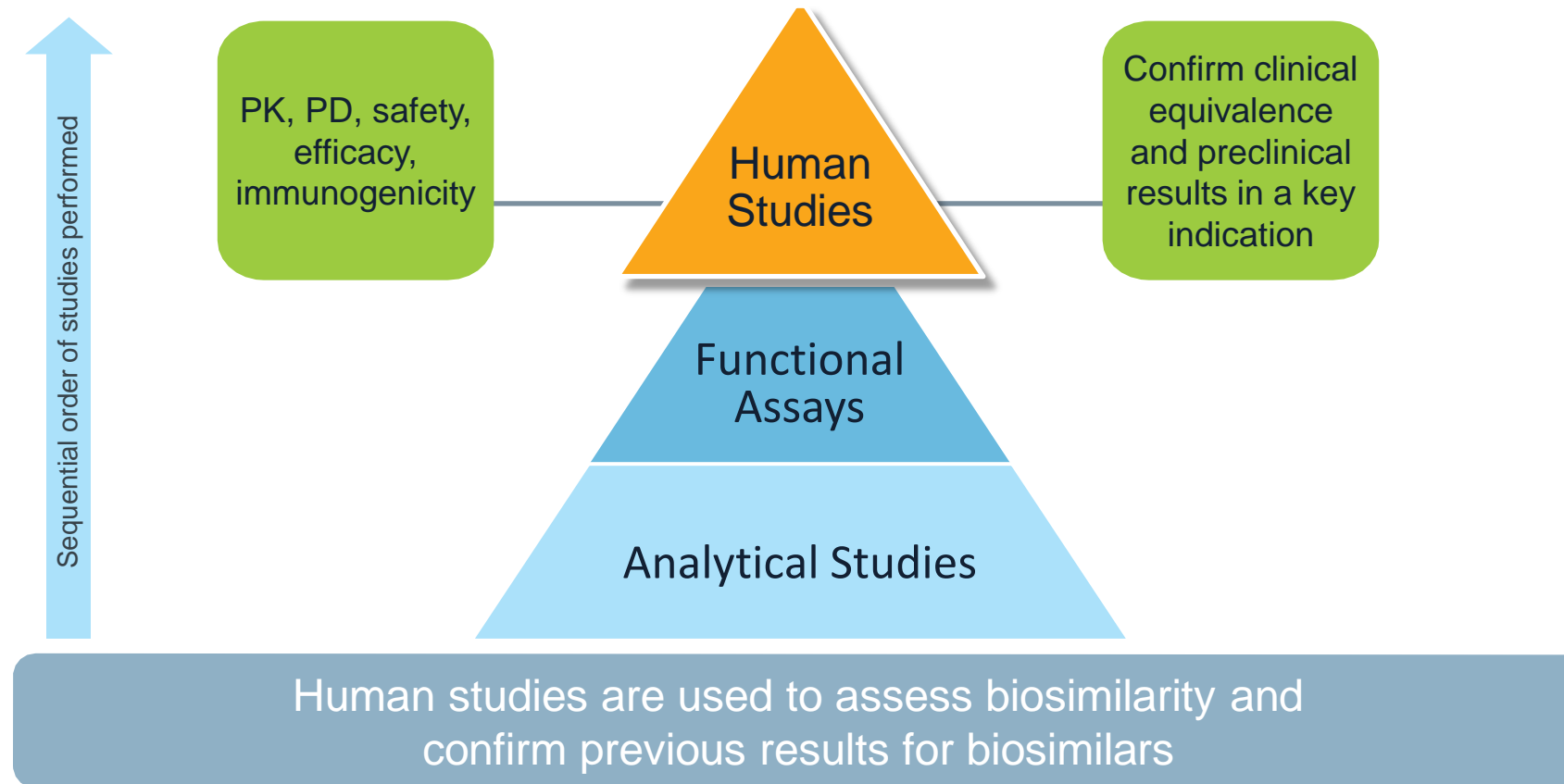


Immunogenicity
assessment



Additional clinical
studies as needed

The development pathways for biosimilars are rigorous but abbreviated compared with development pathways for originator biologics



Evaluate pharmacokinetics and pharmacodynamics

Pharmacokinetics (PK): what the body does to a drug

(Absorption, distribution, metabolism, and excretion (ADME))

Pharmacodynamics (PD): what the drug does to the body

(The treatment's biochemical and physiologic effects on the body)

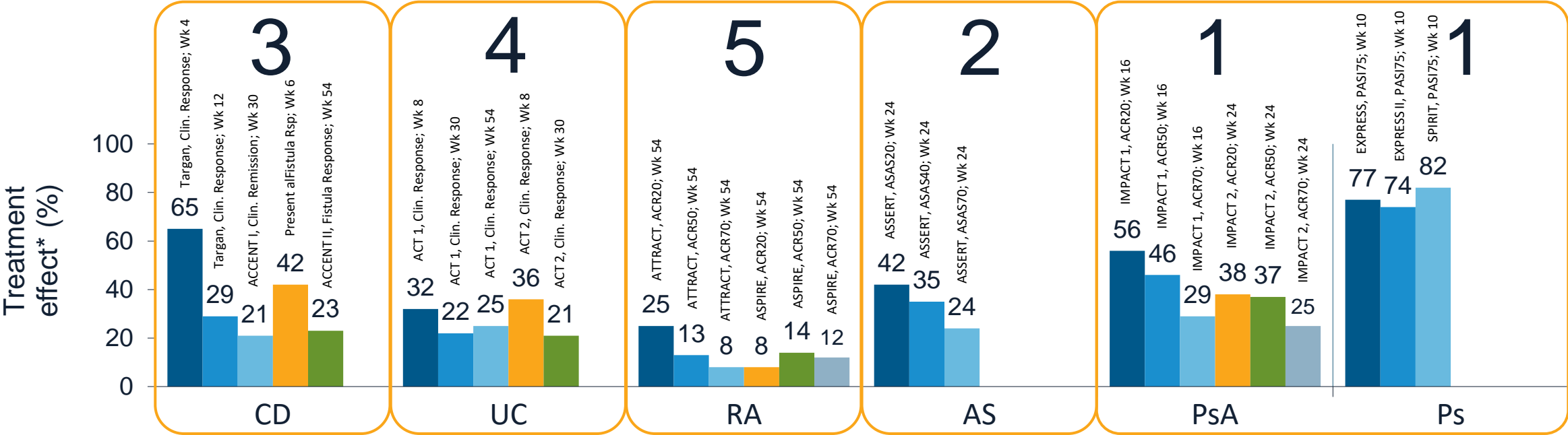
For biosimilars, highly similar PK or PD alone is generally **insufficient** to establish “bioequivalence,” as they are large & complex proteins with unique manufacturing processes

Clinical efficacy, safety, and immunogenicity relative to reference product → Identify the most sensitive study population

The choice of study population must be *sensitive enough* to detect potential clinically meaningful differences between the biosimilar and its reference product¹⁻⁴

- The “most sensitive” population within the “most sensitive” indication should be selected → largest placebo-adjusted difference

Treatment Effect of Infliximab in Different Approved Indications⁵



1. FDA Guidance for Industry. Scientific Considerations in Demonstrating Biosimilarity to a Reference Product. HHS FDA/CDER/CBER, Apr 2015; 2. EMA CHMP Guideline on Similar Biological Medicinal Products, Oct 2014; 3. WHO Guidelines on Evaluation of Similar Biotherapeutic Products. Geneva, 19–23 Oct, 2009; 4. EMA CHMP Guideline on Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins as Active Substance: Non-clinical and Clinical Issues, Jan 2015; 5. Adapted from: Lee. AAPS J 2014;16:22–6; AAPS J 2015;17:1520–1



Immunogenicity is “rigorously” tested for all biological products

Immunogenicity has the potential to **compromise efficacy** by preventing drug binding at the target site¹

Immunogenicity can **cause safety concerns**, including anaphylaxis and neutralization of endogenous proteins¹

Immunogenicity is assessed extensively because it can arise from any biological product and has the potential to influence efficacy and/or safety^{1,2}

But immunogenicity is different in IBD due to PK and use of MTX in RA

Extrapolation of Biosimilar Efficacy and Safety Data: A key component of Biosimilar Approval Process to reduce developmental costs

Extrapolation

- Clinical trials in one indication used as rationale for clinical use in other indications for which the originator biological product is approved¹
- Requires appropriate scientific justification¹

Extrapolation May Be Possible If...

1. Overall similarity with originator biological product is demonstrated based on the totality of the evidence²
2. Clinical similarity is demonstrated in a key indication²
3. Discussion of product MoA and pathophysiology of the conditions involved supports justification³⁻⁵

1. US FDA. Biosimilars: Questions and answers regarding implementation of the Biologics Price Competition and Innovation Act of 2009. 2012. 2. Weise M et al. Blood 2012;120:5111–5117. 3. US FDA. Scientific considerations in demonstrating biosimilarity to a reference product. 2012. 4. EMA. Guideline on similar biological medicinal products containing biotechnology- derived proteins as active substance: non-clinical and clinical issues. 2013. 5. Health Canada. Information and submission requirements for subsequent entry biologics (SEBs). 2010.

Post-Marketing Pharmacovigilance

Monitoring, detecting and prevention of adverse events or drug-related problems

- Consistent manufacturing methods
- Monitoring for immunogenicity
- Post-marketing surveillance
- Unique naming of biosimilar to be distinct and identifiable from reference product
 - Shared core name with distinguishing suffix:
 - “**infliximab-dyyb**” “**infliximab-abda**”
 - “**adalimumab-atto**” “**adalimumab-adbm**”



Meet FDA's
rigorous standards
for approval



Are manufactured
in FDA-licensed
facilities



Are tracked as part
of post-market
surveillance to ensure
continued safety

Key Considerations

- Biosimilars cannot be considered generic biologics.
- Biosimilar development and approval is based on the totality of evidence:
 - Designed to demonstrate biosimilar is highly similar to RP
 - Not to independently establish its safety and effectiveness
- Manufacturers use a stepwise approach to demonstrate biosimilarity:
 - Similarity in structure and function
 - Scientific rigor and state-of-art analytics to identify any differences in “Critical Quality Attributes” to ensure desired quality
 - Taking into account safety and efficacy
- Small structural differences are permitted provided no impact biologic function, clinical safety or efficacy.
 - Small structural differences reconciled in studies demonstrating differences are not clinically meaningful
- Because immunogenicity is unpredictable, assessment of a biosimilar must be based on:
 - A thorough risk-benefit analysis
 - Robust post-marketing risk management programs such that physicians and pharmacists remain alert to unexplained changes in drug efficacy or side effects