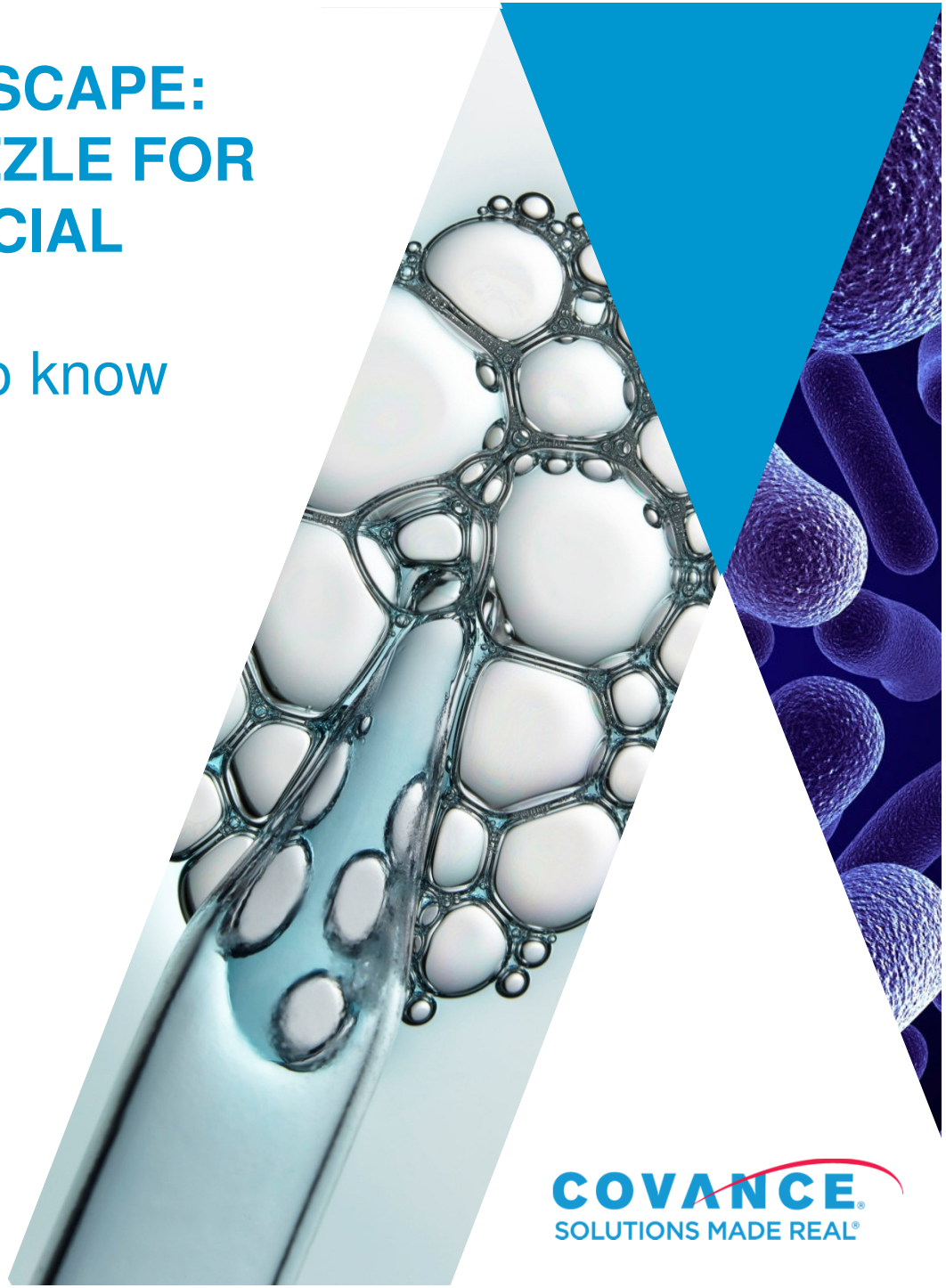
THE BIOSIMILARS LANDSCAPE: KEY PIECES OF THE PUZZLE FOR CLINICAL AND COMMERCIAL SUCCESS: 2017-2021

What all developers need to know



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Covance Inc.

Biosimilars webinar
March 27, 2017

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U.S. Biosimilar Headlines – 2016-2017

APR

FDA Approves Inflectra, a Biosimilar to Remicade

Source: FDA press release. April 5, 2016

AUG

FDA Approves Third Biosimilar in U.S., First for Amgen's Blockbuster Enbrel

Source: Regulatory Affairs Professionals Society. August 30, 2016

SEP

Amgen's Amjevita Approved as First Biosimilar to AbbVie's Humira

Source: The Pink Sheet. September 23, 2016

OCT

Remicade Biosimilar to Launch in November, 15% Cheaper Than Innovator

Source: InsideHealthPolicy. October 17, 2016

NOV

AbbVie Patent Claims Advance, Amgen Humira Biosimilar Delayed

Source: Bloomberg BNA. November 2, 2016

Mylan Seeks FDA Approval for Biosimilar Herceptin Copy

Source: FiercePharma. November 8, 2016

JAN

Supreme Court to Hear Case That Affects How Quickly Biosimilar Drugs Are Marketed

Source: ABA Journal. January 13, 2017

FDA Calls for Switching Studies in Draft Interchangeability Guidelines

Source: BioPharma-Reporter.com. January 17, 2017

Biosimilars: Postmarketing Data Not Enough for Interchangeability

Source: The Pink Sheet. January 17, 2017

Sandoz Head: Enbrel Biosimilar Erelzi Won't Launch Before 2018, Delayed by Legal Battle

Source: FiercePharma. January 25, 2017

FEB

Genentech Fighting to Delay Looming Market Entry of Amgen's Avastin Biosimilar

Source: Seeking Alpha. February 16, 2017

MAR

Genentech Biosimilar Suit Tossed After Just 2 Weeks

Law360. March 1, 2017

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Why Are Biosimilars Making So Much News in the U.S.?

Relatively new approval pathway

- Pathway created in 2010, first biosimilar (Zarxio) approved in 2015

Controversial reimbursement policy

- All biosimilar versions of the same reference product will share the same billing code and Medicare payment rate

Increasing scrutiny of high drug prices

- Would seem to make biosimilars more attractive to providers, patients, payers

Patent cliff, revenue potential

- Size of U.S. biosimilar market expected to increase significantly over the next few years

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Overview

What are biosimilars?

Regulatory

- Overview of development pathway and update on key issues in 2017-2021

CMC/bioanalytics/PD

- Extensive experience can shorten time to Go NO GO

Cost-effective (fit for purpose) preclinical tox program

Key clinical issues

- PK equivalence
- Planning/execution of phase III equivalence study

Early initiation of market access/commercialization messages

Summary/questions

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What Are Biosimilars?

Biologics Price Competition & Innovation Act (BPCI Act) of 2009

- Part of the Affordable Care Act
- Created an abbreviated licensure pathway for biological products shown to be biosimilar to or interchangeable with an FDA-licensed reference product
- The biological product is highly similar to the reference product notwithstanding minor differences in clinically inactive components;
- There are no clinically meaningful differences between the biological product and the reference product in terms of the safety, purity and potency of the product

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EU Directive 2004/27/EC

- A biosimilar is a biological medicinal product that contains a version of the active substance of an already authorized original biological medicinal product (reference medicinal product)
- A biosimilar demonstrates similarity to the reference medicinal product in terms of quality characteristics, biological activity, safety and efficacy based on a comprehensive comparability exercise

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Biologic Products Being Targeted by Biosimilars in Development*

Target product	Company	Therapeutic area	Est. # of biosimilars in development globally
Avastin® (bevacizumab)	Roche	Colorectal, cervical, kidney, ovarian and non-small cell lung cancer, glioblastoma	15
Humira® (adalimumab)	AbbVie	Ankylosing spondylitis, Crohn's disease, juvenile idiopathic, psoriatic and rheumatoid arthritis, ulcerative colitis	13
Herceptin® (trastuzumab)	Roche	Breast and stomach cancer	21
Remicade® (infliximab)	Merck / Johnson & Johnson	Ankylosing spondylitis, Crohn's disease, psoriasis, psoriatic and rheumatoid arthritis, ulcerative colitis	13
Rituxan® (rituximab)	Roche	Non-Hodgkin's lymphoma, leukemia, polyangiitis, rheumatoid arthritis	35

**Amgen 2015 Trends in Biosimilars Report*

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Stepwise Assessment for Totality of Evidence

Quality (Structure & Function) → Pharmacology → Clinical

- Must have the same protein sequence and demonstrated potency
- Minor differences in post-translation modifications (e.g. glycosylation)
  - Relevance determined through functional assessments
- Should have same effector functions regardless of potential contribution to MOA

RESIDUAL UNCERTAINTY POTENTIAL FOR CLINICAL DIFFERENCE

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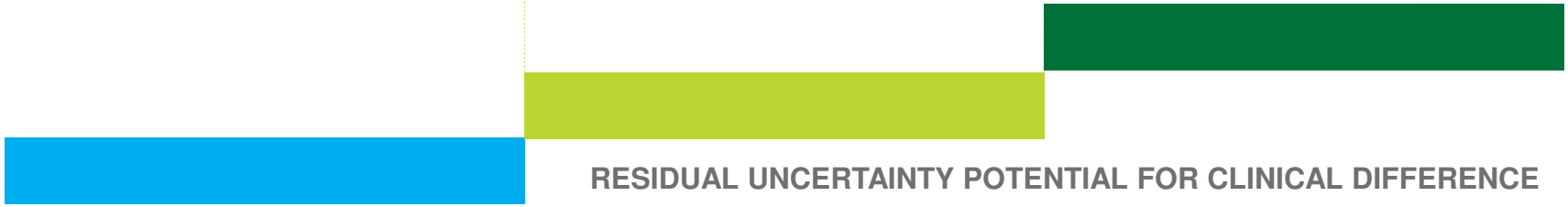
Stepwise Assessment for Totality of Evidence

Quality (Structure & Function) → **Pharmacology** → Clinical

- Pharmacokinetics (PK) in healthy volunteers
  - Most sensitive population
- Equivalent PK establishes same dose as reference product assuming equivalent potency and functions
  - Generally 90% CI to be within 80-125% as standard
- Pharmacodynamics (PD) with dose-response equivalence can infer clinical efficacy



RESIDUAL UNCERTAINTY POTENTIAL FOR CLINICAL DIFFERENCE

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Stepwise Assessment for Totality of Evidence

Quality (Structure & Function) → Pharmacology → **Clinical**

- Clinical efficacy confirmed in a randomized, blinded, head-to-head study in a sensitive population with sensitive endpoint(s)
- Clinical safety confirmed in at least one sensitive patient population (e.g. use as monotherapy); with enough exposure/time
- Immunogenicity assessed with drug tolerant assays in sensitive population (e.g. no immune suppression or concomitant chemotherapy)

RESIDUAL UNCERTAINTY POTENTIAL FOR CLINICAL DIFFERENCE

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Stepwise Assessment for Totality of Evidence

- Each step provides a critical contribution to the overall totality of evidence
- Each step should rely on the most sensitive state-of-art capabilities
- No step can refute/overcome significant differences in other development steps
- Need to satisfy all three steps to demonstrate biosimilarity

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Key to Success

Biosimilars must be systematically engineered to match the reference product

Biosimilarity assessments must be conducted with the innovator reference product at all levels of product development, including:

- Physicochemical attributes
  (primary, secondary, tertiary and quaternary structural assessment)
- Biological activity
- Preclinical in vivo biosimilarity
- Phase I PK & safety
- Phase III efficacy & safety
- Impact of shelf life on all the above is critical

The inherent variability of biosimilars exists in the innovator reference product as well. Important to decipher how these differences impact clinical outcome

- The characterization of the biosimilar will always be much higher than that of a new biological entity

Characterization will always include reference product vs. biosimilar

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Key Issues in Biosimilar Development Process and Clinical Practice

Process	Issue	Potential solutions
Sourcing reference product for U.S. submission	Use of non-U.S.-licensed reference product in clinical biosimilarity studies (Phase III)	Likely three-way bridging clinical PK and/or PD study
Extrapolation (of indications beyond those studied)	Getting full range of indications in the reference's label without conducting efficacy studies	Supported by regulatory guidance, provided that the efficacy and safety of the biosimilar is justified, based on the overall evidence of biosimilarity provided and adequate scientific justification
Substitution (of originator for biosimilar or between biosimilars)	Unintentional or automatic substitution by pharmacists	Regulatory measures to define automatic substitution policies

1 After Table III from : M Khraishi,, et.al. Biosimilars: AMultidisciplinaryPerspective. Clinical Therapeutics/38(5) 2016, 1238-1249

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Key Issues in Biosimilar Development Process and Clinical Practice[1]

Process	Issue	Potential solutions
Switching/ interchangeability	Safety and efficacy effects of switching or alternating to and from biosimilars and their reference products	Considerations in Demonstrating Interchangeability With a Reference Product (2017 FDA draft guidance[2]): • Switching study designs • Carefully consider product presentation • Requirements will vary based on the product submitted • Early agency engagement encouraged
Post-marketing pharmacovigilance	Confusion in naming for AE drug reports	Appropriate measures to identify product brand name and batch number Regulatory bodies adopt and approve risk-management plans to include specifically focused post-marketing studies
Real-world acceptance/ reimbursement	Limited understanding of biosimilars/their stringent development requiring a comparative assessment. Concern re: safety and efficacy	Physician education; provide reimbursement process analysis/commercialization; value proposition

1 After Table III from : M Khraishi,, et.al. Biosimilars: A multidisciplinary Perspective. Clinical Therapeutics/38(5) 2016, 1238-1249
2 https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf

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Regulatory Update: Focus on India and China

India and China are significant producers in the world biosimilars market.

India 

- Revised guidance document released in 2016
- Poised for big growth – expected increase from $186 million in 2016 to $1.1 billion in 2020 according to industry estimates
- Indian firms investing in biosimilar development including establishing manufacturing facilities in other countries

China 

- Analysts see substantial growth opportunities for monoclonal antibodies in the next five years
  - Approximately 5.5 million RA patients in China that cannot afford using drugs from global companies
- Technical guidance release in 2015 – but it is not derived from any overarching law
- No abbreviated approval pathway - biosimilars are subject to the same approval pathway as innovative biologics

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Regulatory - Summary

- EMA and FDA have become more harmonized, but there are still several important differences; regulatory requirements continue to evolve
- Many clients approaching Covance to bid on biosimilar studies do not fully understand the regulatory landscape
- Covance recommends early client engagement to partner on prep and conduct of agency meetings

EARLY ENGAGEMENT TO GUIDE CLIENTS THROUGH REGULATORY LANDSCAPE IS KEY TO REDUCING TIME AND COST

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CMC Analytics-Comparability

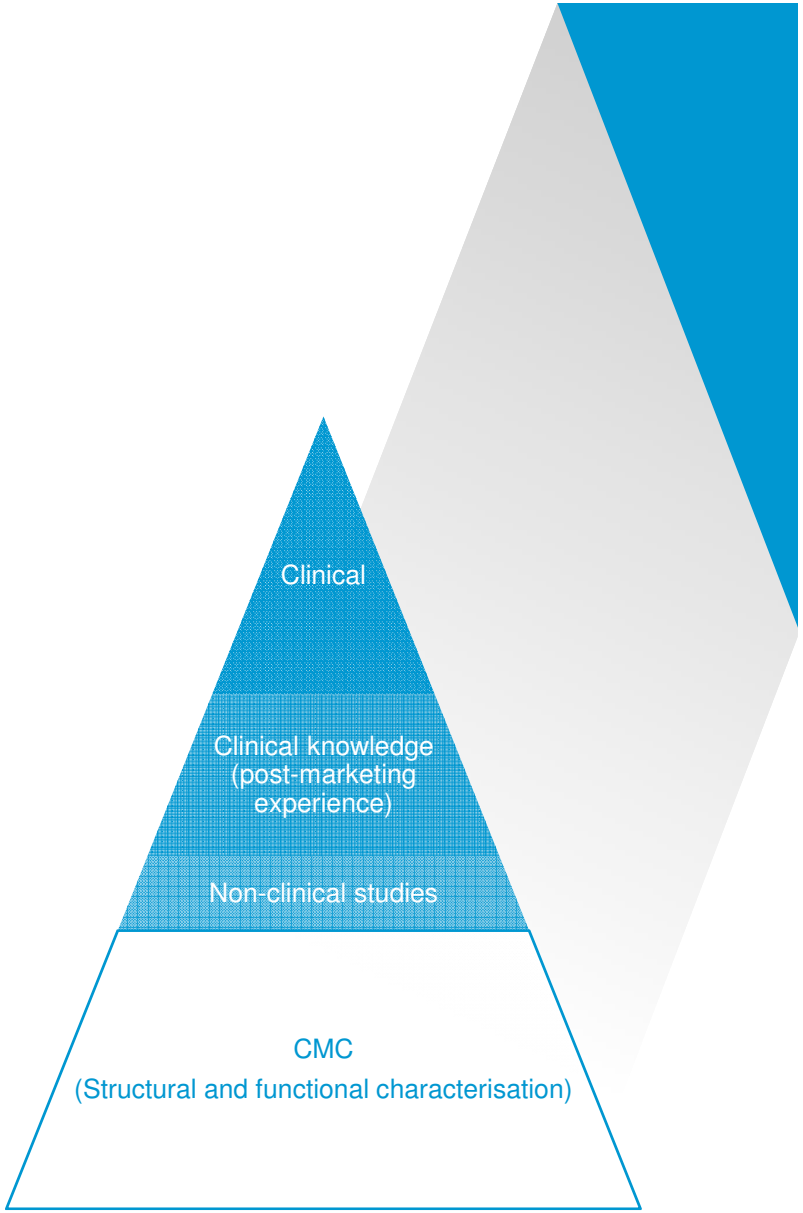
CMC WILL MITIGATE RISK FACTORS

EFFICACY
- Potency
- Effector function
  - ADCC
  - CDC
- Glycosylation
- Oxidation
- Deamidation
- Aggregation

SAFETY
- Aggregation
- Deamidation
- Oxidation
- Glycosylation

IMMUNOGENICITY
- Glycosylation
- Aggregation

PK
- Aggregation
- Glycosylation



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Adalimumab Biosimilar

CASE STUDY – ASIA-BASED COMPANY

Developing an adalimumab (Humira) biosimilar

Came to Covance with potential cell clones expressing adalimumab.

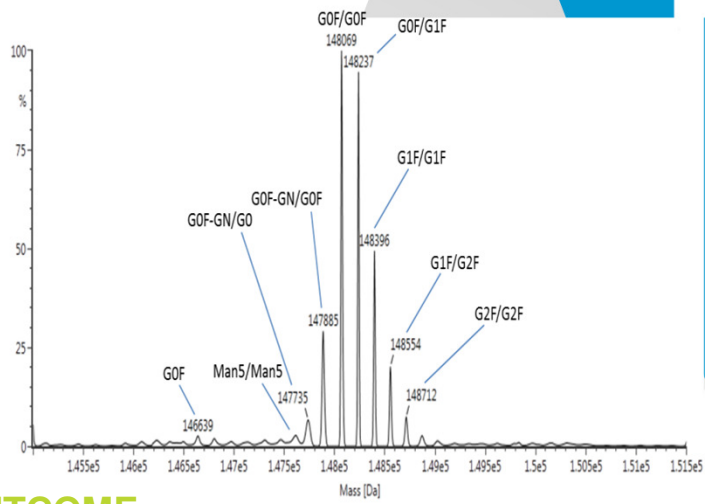
Covance tasked to help them select best clone to minimize development risk

- **Designed an analytical program based on the TPP**
- **Worked out the preliminary clinical quality attributes (CQAs)**

Reviewed all their clone data:

- **Identified differences in the Glycosylation profiles across the clones**
- **Selected the one with most similarity to reference adalimumab (Humira)**

Glycosylation profile of adalimumab



OUTCOME

Although small differences were observed even in the selected clone, there was confidence in the selection due to an understanding of the CQA and a risk assessment of impact on MOA.

Covance has extensive experience in constructing a CMC strategy around linking a biosimilars structure and function to its likely clinical PK/PD and efficacy.

Covance added value for this client by helping them select the best clone to carry forward.

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Cost-Effective (Fit-for-Purpose) Nonclinical Testing: Position

Testing (same for Mab or a non-Mab proteins) involves biological activity/nonclinical biosimilarity to marketed (innovator) drug

- However, no need to be too creative as making a biosimilar and not a new biological

A range of regulatory guidelines exist to assist nonclinical development (e.g., EU, FDA, WHO)

Key is stepwise approach to testing:

- Step 1 = relevant in vitro work (e.g. binding/functional assays)
- Step 2 = determine if in vivo work needed
- Step 3 = if yes, case-by-case PK and/or PD study and/or toxicology study

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Nonclinical Testing: Strategy

Often a key area of discussion is need for toxicology testing, as no global agreement:

- EU indicates that toxicity testing is usually not recommended
- FDA says testing can be discussed including justifications for not conducting a toxicity study
- WHO (and some regional guidelines) currently request testing in at least one repeat dose toxicity study [NOTE: WHO guideline currently being revised to be in line with EU]
- Thus, toxicology work for demonstrating biosimilarity to the reference product is still occurring (including NHP studies for Mabs) due to need to satisfy requirements of all potential markets

Goal is not to perform toxicology studies – comparability in support of biosimilarity can be made through physio-chemical and in vitro characterisation (and/or in vivo PK/PD examination)

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Phase I Pivotal Success Factors

EXPERTISE

- Highly experienced bioanalytical lab (PK and ADA)
- Significant internal medical/scientific biosimilar expertise
- Highly experienced in bioequivalence (BE) studies
- Strong track record of program transitions(Phase I to III)

TIME

- Rapid startup times
- Comprehensive U.S. & EU operational capabilities
- Highly effective collaboration between CRU and BioA lab
- Dedicated early clinical services biometrics team

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Planning/Execution of Phase III

POINTS TO CONSIDER/UNIQUE CHALLENGES

Usually required to further demonstrate biosimilarity (i.e. the highly similar nature) of the two products (biosimilar vs. branded) re.: safety and effectiveness

Designed to demonstrate "biosimilarity," not safety and efficacy de novo

Key design issues include:

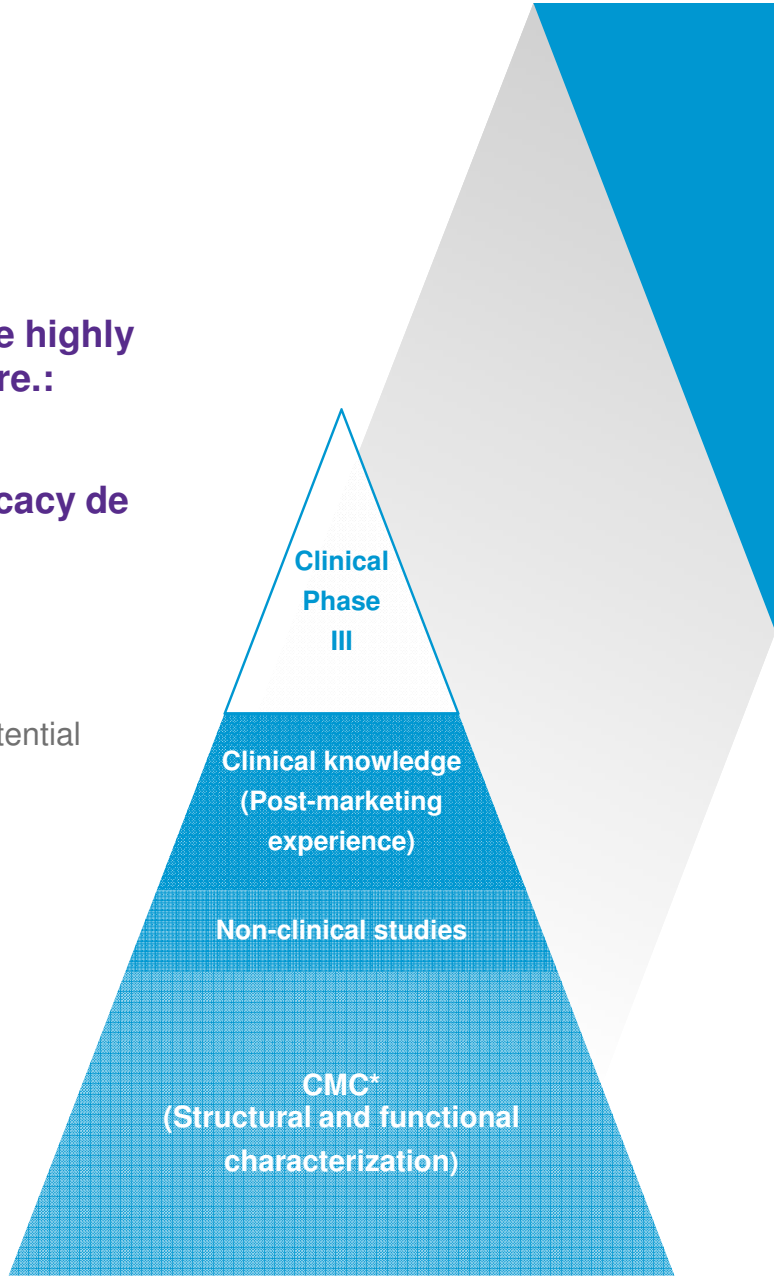
- Therapeutic indications
- Choice of target patient population (most sensitive to show any potential differences)
- Background therapy
- Blinding, stratification
- Switch from originator to biosimilar product

Primary endpoint variable

Choice of equivalence vs. non-inferiority design

- Selection and justification of equivalence margin

Consideration of alternative statistical approaches for greatest efficiency



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Summary of Covance Biosimilars Development Experience (2010-16)

Generic Name	Number of Unique Biosimilars	Number of Individual Projects
Inflammatory Mabs Abatacept Adalimumab Etanercept Infliximab Omalizumab Rituximab Tocilizumab	37	59
Non-inflammatory biologics Mab Insulins Liraglutide EPOs FSH Somatropin	59	93
	96	**152**

Covance has significant and broad biosimilars experience across the full spectrum of drug development:

CMC/bioanalytical
Exploratory/preclinical
Market access/reimbursement
Clinical/labs

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Clinical Expertise/Experience in Rheumatology/Autoimmunity/Inflammation

- Significant internal medical/scientific rheumatology drug development (RA, SLE, others)
- Phase Ib-IV trial experience in RA
- Strong track record of smooth program transitions (Phase I to III)
- Proprietary databases identify high performing sites, motivated/have interest in biosimilar studies

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Market Access Considerations for Biosimilar Development

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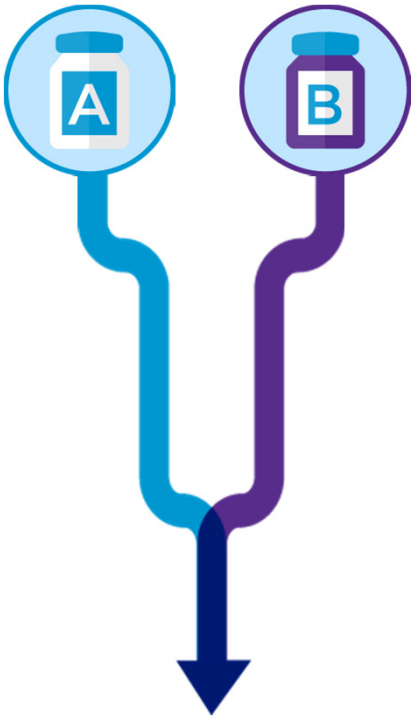
Market Access Planning



- In many ways, the commercial path for biosimilars will be as challenging as that for a unique innovator biologic
- In order to facilitate market access for biosimilar products, manufacturers will need to engage in the full spectrum of market access and health economic planning activities
- Manufacturers should begin these activities early in clinical development

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Medicare Part B Reimbursement for Biosimilars Depends on the Regulatory Pathway

Full Biologics License Application (BLA)

- Follow-on biologics that essentially are biosimilars to an innovator product, but do not have to demonstrate biosimilarity
- Technically not biosimilars
- Eligible to receive distinct HCPCS code and ASP payment rate

Teva's Granix (tbo-filgrastim) – "Biosimilar" of Neupogen (filgrastim)

Abbreviated Biosimilar Pathway

- Biosimilars approved under new FDA pathway created by the ACA
- *Medicare payment equal to biosimilar ASP* + 6% of the ASP of the reference product*

Sandoz's Zarxio (filgrastim-sndz)
Reference product: Neupogen

Celltrion's Inflectra (infliximab-dyyb)
Ref. product: Remicade (infliximab)

Sandoz's Erelzi (etanercept-szzs)
Ref. product: Enbrel (etanercept)

Amgen's Amjevita (adalimumab-atto)
Ref. product: Humira (adalimumab)

Abbreviated Biosimilar Pathway With Interchangeability

- Biosimilars approved under new FDA pathway that also have been deemed interchangeable by the FDA
- May be subject to automatic substitution at the pharmacy
- *Medicare payment equal to biosimilar ASP* + 6% of the ASP of the reference product*

TBD

"Biosimilar ASP" is the weighted-average ASP of all biosimilar versions of the same reference product.

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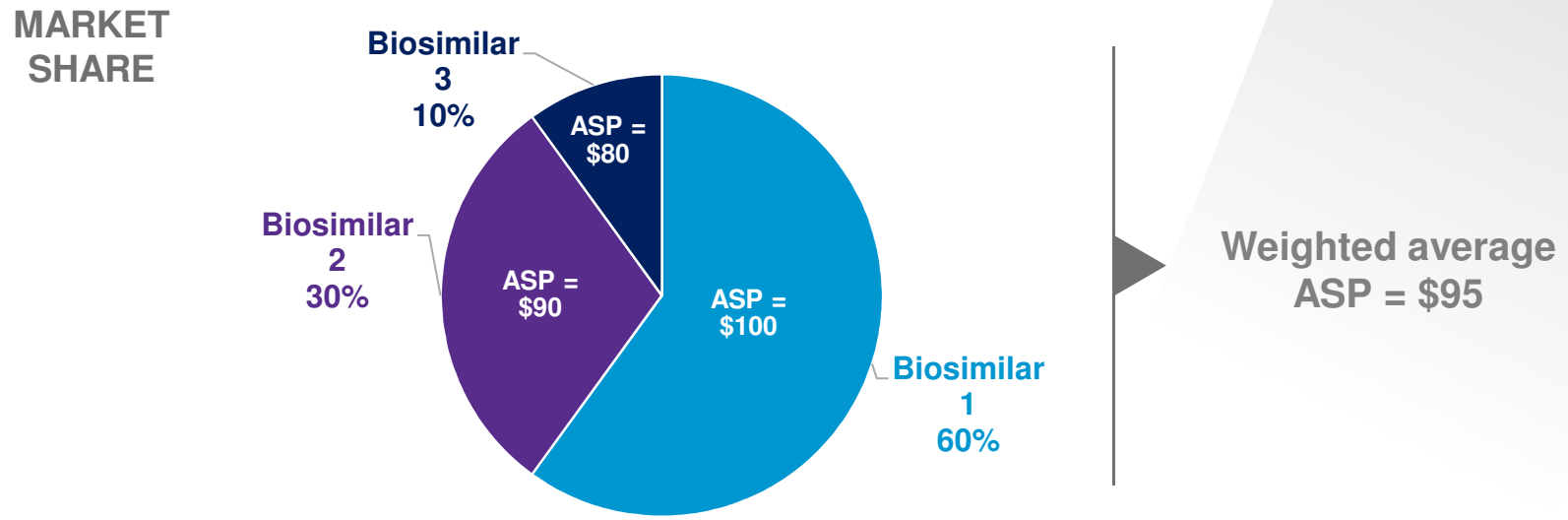
All Biosimilar Versions of a Given Reference Product Will Share the Same HCPCS Code and ASP Payment Rate

EXAMPLE

- The weighted-average ASP for a HCPCS code describing three biosimilar versions of the same reference product could be calculated as follows:



The biosimilar version with the most market share will have the most influence on the weighted average ASP.

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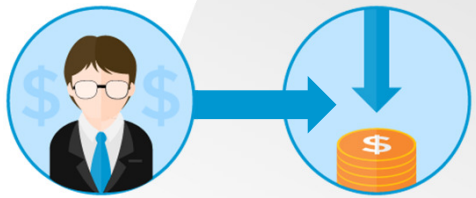
Covance Primary Research with Commercial Payers

COVANCE CONDUCTED A THREE-PHASE SURVEY OF COMMERCIAL PAYER DECISION-MAKERS FROM PLANS COVERING A COMBINED TOTAL OF OVER 100 MILLION COVERED LIVES

- The first phase of the survey addressed payer insights regarding coverage of biosimilars and examined the impact of factors such as:
  - therapeutic area (specifically, oncology and rheumatoid arthritis [RA])
  - type of FDA approval (BLA vs. abbreviated pathway)
  - interchangeability
  - pricing
- The second phase of the survey focused more on reimbursement methodologies, coding and clinical trial data requirements
- The third phase of the survey (conducted in early 2016) specifically addressed current coverage of Neupogen and Zarxio



Overall, the survey results indicate that **commercial payers are willing to steer utilization toward lower-cost biosimilars**, especially if they are viewed as interchangeable.

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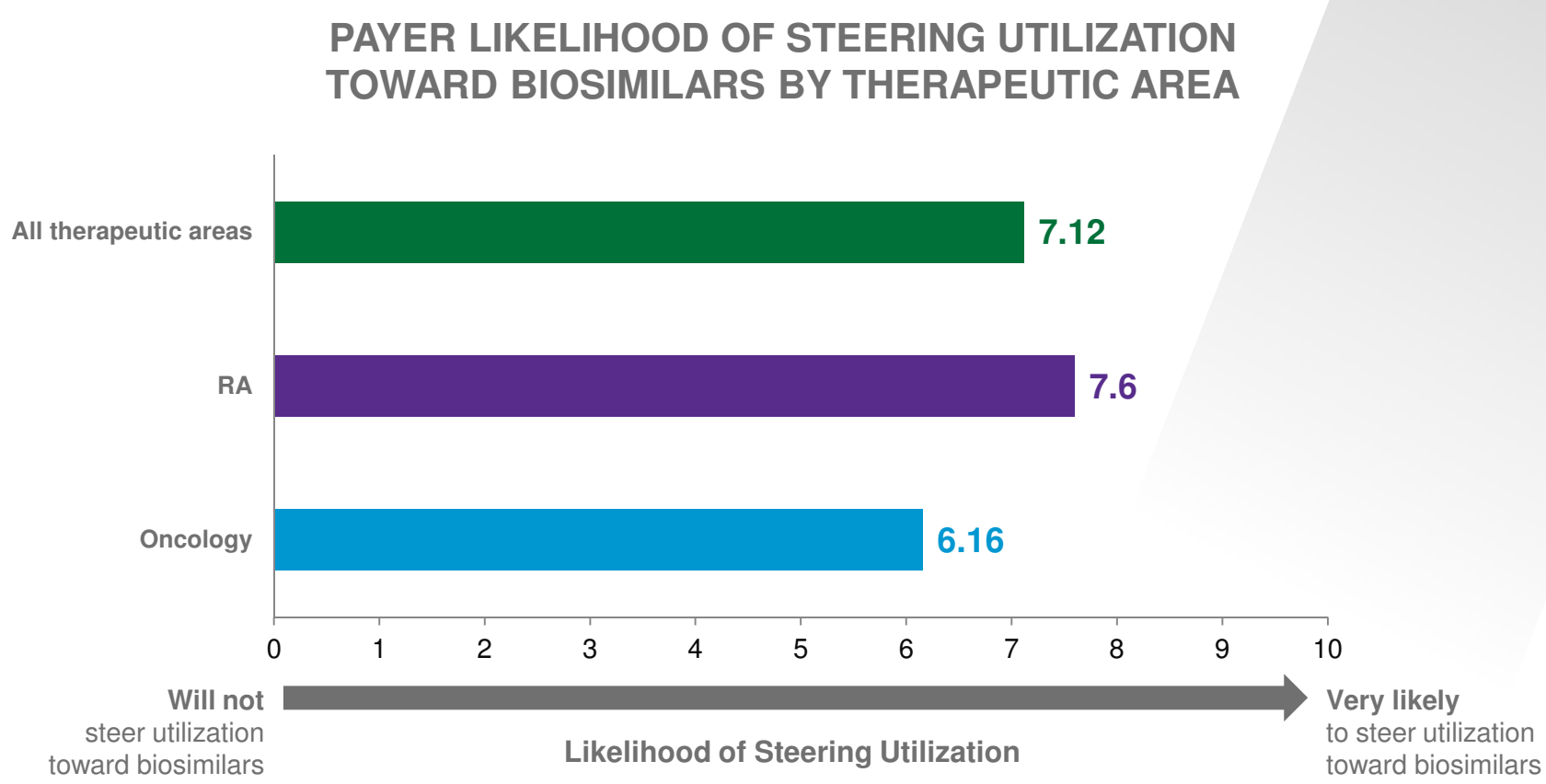
Plans Are More Likely to Steer Utilization Toward Biosimilars in RA Than in Oncology



Source: Covance data on file, 2013-2015.

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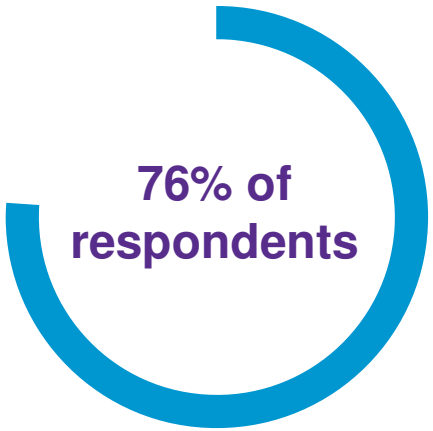
Payers May Consider a Biosimilar to Be Interchangeable Based on Factors Other Than FDA Designation

- As previously mentioned, payers ranked FDA interchangeability designation as one of the top two factors in coverage decision-making for biosimilars
- However, **76% of respondents** indicated that they would be willing to consider a biosimilar to be interchangeable even if it has not received a formal designation by the FDA, based on sources of information such as the following:



- **Compendia listings**
- **Clinical trials**
- **Clinical evidence demonstrating efficacy and safety**
- **NCCN guidelines**
- **CMS coverage decisions**
- **KOL input**
- **Additional supporting documentation**

Source: Covance data on file, 2013-2015.

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Customer Support Programs

- To compete with market-leading innovator products, biosimilar manufacturers will need to provide **robust customer support** resources:

Reimbursement support

Financial support

Provider education

- The need for these resources will be especially **important during the initial post-launch period**, when new products face the most access challenges.

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Covance Key Strengths

- Presence of strategic regulatory group and strong understanding of the changing regulatory environment globally
- New CMC knowledge/experience/visibility with many biosimilar companies
- Integrated Phase I/III protocol designs/programs experience
- Phase IV observational study design and execution experience
- Understand the importance of early engagement of the CMA group to navigate the payer and prescriber complexities through to successful commercialization

INCREASING ACTIVITY AND EXPERTISE ACROSS THE FULL SPECTRUM OF BIOSIMILAR DEVELOPMENT IS UNIQUE AMONG CROs

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Q&A Session

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