

THE BIOSIMILARS LANDSCAPE: STRATEGIES FOR CLINICAL AND COMMERCIAL SUCCESS

What all developers need to know

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The field of biosimilars is expanding rapidly. They provide an opportunity for cost savings for key stakeholders, and for pharmaceutical and biotech companies to control a share of the market as the patents for blockbuster biologic drugs expire.

Biosimilars are a relatively new area of the market with challenges that require sufficient knowledge, experience and infrastructure to ensure smooth and successful progression through the development life cycle.

This white paper discusses important considerations for embarking upon a biosimilars development program, including critical steps in their manufacturing, the current biosimilars regulatory environment and challenges in market access.

Critical Steps in Development to Ensure Biosimilarity

Biosimilars are versions of biological medicinal products that demonstrate similarity to licensed (innovator) products, or reference medicinal products. To be approved as a biosimilar the molecule must be highly similar to the reference product in terms of quality characteristics, safety and efficacy.

The development of biosimilars involves three steps that need to be completed to demonstrate biosimilarity (Figure 1). The chemical, manufacturing and control (CMC) strategy to ensure structural and functional biosimilarity is the most crucial step. A successful CMC strategy reduces development risk.

The CMC strategy includes several steps, beginning with defining the critical quality attributes (CQAs) of the molecule in the context of the mechanism of action (MoA), establishing analytical methods to assess these and then understanding the lot-to-lot variability of the innovator product with respect to these CQAs. This knowledge then enables selection of the most appropriate cell clone to express the biosimilar, and optimization of the manufacturing process.

Covance is highly experienced in establishing CMC strategies for biosimilar development, an example of which is presented in the case study below. The outcome of the CMC analytical biosimilarity assessment determines the extent of nonclinical and clinical studies that are then required to assess biosimilarity in safety and efficacy.

Quality (structure and function)

- ▶ 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

Pharmacology

- ▶ 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 to 125% as standard
- ▶ Pharmacodynamics (PD) with dose-response equivalence can infer clinical efficacy

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)

Figure 1. Stepwise assessment for biosimilar development is required to demonstrate biosimilarity.

Case study: Applying a methodical CMC approach to lower biosimilar development risk

CMC strategy to minimize development risk: Selecting the right clone

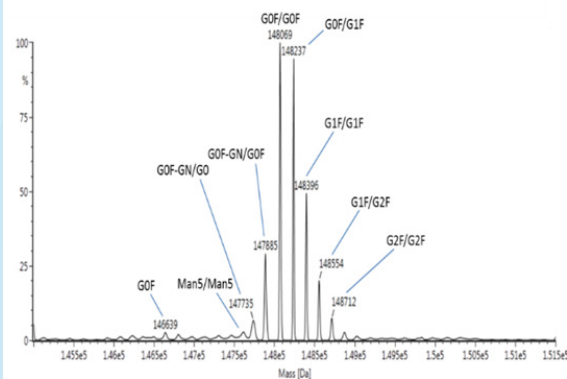
Situation

- ▶ A Europe-based company had many potential clones expressing adalimumab
- ▶ Covance was tasked with advising on the best clone to minimize development risk.

Actions

- ▶ Designed an analytical program based on the target product profile
- ▶ Determined the preliminary CQAs
- ▶ Reviewed all data from the clone:
 - Identified differences in glycosylation profiles
- ▶ Selected the clone with highest similarity to adalimumab

Glycosylation profile of adalimumab



Results

Although small differences were observed in the selected clone, there **was confidence in the selection** due to an **understanding of the CQAs** and a **risk assessment of the impact on MoA**

Dynamics and Complexities of the Biosimilars Regulatory Environment

Current EMA and FDA guidelines are largely harmonized, but several important differences remain as the regulatory requirements for biosimilars continue to evolve. The main difference between the FDA and EMA in regards to biosimilar approval is their assessment of interchangeability: the FDA determines interchangeability between a biosimilar and its reference product in their regulatory review, while the EMA defers it to the individual member states.

Two of the countries with the largest expansion in biosimilars development worldwide are China and India, where significant growth is expected in the coming years: India's biosimilars market is estimated to reach \$1.1bn by 2020. In India, a revised guidance document for biosimilars development was published in 2016; in China, biosimilars are required to undergo the same approval process as innovative biologics.

Regulatory Guidance on Nonclinical Testing

After the extent of CMC biosimilarity has been determined, the residual safety risk is then assessed. This informs the extent of a nonclinical program, and the study designs if required. The EMA, FDA and WHO provide recommendations on the nonclinical development of biosimilars. These guidelines recommend that the focus of testing should include the demonstration of similarity in terms of biological activity to the reference product, and should use a stepwise approach:

- ▶ Step 1: Complete relevant in vitro work, such as target binding or functional assays
- ▶ Step 2: Determine if in vivo work is required
- ▶ Step 3: If in vivo work is needed, complete a case-by-case pharmacokinetic (PK) and/or pharmacodynamic (PD) and/or toxicology study

Currently there is no global consensus on the need for toxicology studies for biosimilars: EU guidelines (and soon those of the WHO) indicate that toxicology testing is not usually recommended, while FDA guidance states that toxicology testing can be discussed.

Although in vivo toxicology work is currently being undertaken in the biosimilar field to satisfy global development requirements, the long-term goal is to conduct these studies only if there is a scientific need based on the assessment of residual safety risk. Therefore, it is important to have a robust CMC analytical strategy to enable better assessment of biosimilarity and provide support for reducing the number of required toxicology studies.

Market Access Considerations for Biosimilars Development

Successfully navigating the path to success with any new biosimilar product requires a coordinated approach to market access and health economic planning activities. These include landscape assessments, primary research with stakeholders and researching the policy and insurance environment. At Covance, we recommend these activities begin early in clinical development to ensure the program meets the needs of the target market(s).

In the U.S., biosimilars reimbursement is dependent on which regulatory pathway is followed. Importantly, all biosimilars of a given reference product share the same healthcare common procedure coding system code and average sales price payment rate. The biosimilar version with the largest market share has the most influence on the weighted average sales price.

Market Access Insights

A recent survey of commercial payer decision makers conducted by Covance¹ showed that the majority of respondents (76%) would consider a biosimilar to be interchangeable based on factors other than FDA designation. The survey also highlighted that payers are willing to steer utilization towards biosimilars across many therapeutic areas, but especially in rheumatoid arthritis (RA) (Figure 2).

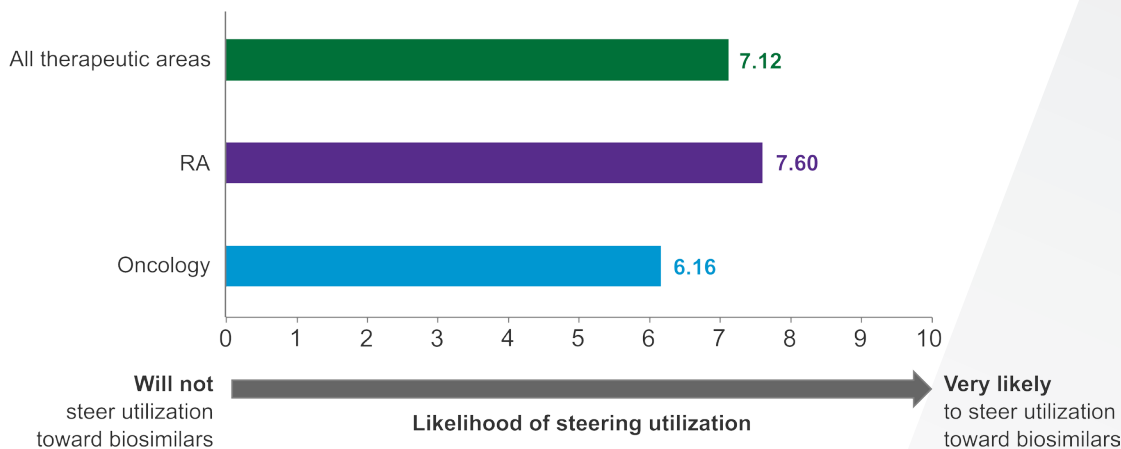


Figure 2: Likelihood of payers steering utilization toward biosimilars rather than the reference product

The survey concluded that it is important for biosimilar manufacturers to provide robust customer service support features to compete with market-leading reference products, especially during the initial post-launch period when new products face the most market access challenges.

Summary of Key Issues Throughout the Biosimilar Development Process

Several issues arise during biosimilar development and their use in clinical practice.² Covance has the expertise to address these complex issues, as well as the design and execution of potential solutions. These may include (but are not limited to) those highlighted in Table 1 below.

Process	Issue	Potential solution(s)
Sourcing reference product for U.S. submission	Use of non-U.S.-licensed reference product in clinical biosimilarity studies (Phase III)	<ul style="list-style-type: none"> ▶ Three-way bridging clinical PK and/or PD study between U.S. reference product, EU reference product, and biosimilar product
Extrapolation (of indications beyond those studied)	Approval of the full range of indications in the reference product's label without conducting efficacy studies	<ul style="list-style-type: none"> ▶ Regulatory guidance supports extrapolation if the efficacy and safety of the biosimilar is justified based on the overall totality of evidence
Substitution (of originator with biosimilar, or between biosimilars)	Unintentional or automatic substitution by pharmacists	<ul style="list-style-type: none"> ▶ Regulatory measures are in place to define automatic substitution policies
Switching/ interchangeability	Concern regarding potential negative effects on safety and/or efficacy of switching or alternating to and from biosimilars and their reference products	<ul style="list-style-type: none"> ▶ Interchangeability determined by the FDA during the review process ▶ Draft guidance from the FDA in <i>Considerations in Demonstrating Interchangeability with a Reference Product (2017)</i>³ outlines considerations for the design of switching studies to provide data on the impact of switching on safety and efficacy
Post-marketing pharmacovigilance	Confusion in naming for adverse event drug reports	<ul style="list-style-type: none"> ▶ Apply appropriate measures to identify product brand name and batch number used in patients ▶ Risk-management plans driven by regulatory agencies will include specifically focused post-marketing studies
Real-world acceptance/ reimbursement	Limited understanding of biosimilars and their stringent development, leading to concerns regarding their safety and efficacy	<ul style="list-style-type: none"> ▶ Educate physicians on biosimilars ▶ Provide reimbursement process analysis and value proposition

Table 1. Summary of the key issues in biosimilar development and a non-exhaustive list of potential solutions

The Covance Approach to Biosimilar Development

Covance knows how to bring biosimilars to market successfully and efficiently, having previously developed 96 unique biosimilars in 152 individual projects. Through this experience we have developed expertise in:

- ▶ Development and execution of a CMC strategy based on an in-depth understanding of the CQAs and structure/function relationship, using appropriate analytical methodologies to assess biosimilarity and the clinical PK, PD, safety and efficacy consequences of differences
- ▶ Navigation of regulatory pathways using in-house experts, who each have up to 30 years' experience with global and local regulatory agencies
- ▶ Early engagement with market access stakeholders, helping to solve payer and prescriber complexities

Multiple biosimilars are being simultaneously developed by rival companies for many licensed products, so the need for efficient development is critical. Partnering with a CRO that has experience in biosimilar development as well as a deep understanding of the unique manufacturing, regulatory, clinical and market access challenges that arise is crucial to succeeding in the highly competitive biosimilar environment.

Covance has a wealth of experience in biosimilar development and understands the associated challenges. We use our expertise in CMC strategy development to identify optimal manufacturing processes and the best clone to move forward with, while engaging key stakeholders early to ensure requirements for each target market are satisfied. Our goal is to help you achieve success in your biosimilar development program.

Learn more about our drug development solutions at www.covance.com

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