ACCELERATING THE BIOSIMILAR JOURNEY
For biosimilar developers, the lure of tapping into a global market estimated by Datamonitor to grow to $3.7 billion by the end of 2015 alone is irresistible. For healthcare systems squeezed by spiraling costs, the spread of lower-priced versions of expensive biologic therapies could cut prescription drug spending. And for patients worldwide, a thriving biosimilars industry promises to make life-changing drugs more accessible.

Despite these driving forces, the introduction of biosimilars has not been an unmitigated success to date. Why? Factors include:

- Technical challenges and investment required to demonstrate similarity
- Lack of a predictable regulatory pathway in the US, a key market
- Highly variable prescriber uptake and market penetration in the EU
- Vigorous defense of their markets by originator companies

PAREXEL has helped spearhead the development of biosimilars, providing regulatory support for more than 20 product development programs, including the first biosimilar monoclonal antibody (mAb) approved in the EU (2013). In fact, we have been involved in more than 60 scientific advice and regulatory agency interactions in the EU, US, Canada, Japan and other regions, and contributed to four successful EU biosimilar marketing authorization submissions (with a fifth underway).

PAREXEL has also helped clients demonstrate pharmacokinetic/pharmacodynamic (PK/PD) and clinical similarity to relevant licensed reference products. We have enrolled more than 6,000 healthy volunteers and patients in nearly 60 early- and late-phase biosimilar trials. Along the way, we’ve learned the key concerns and needs of regulators reviewing biosimilar submissions around the world.

Developing a biosimilar product requires a precise, stepwise fusion of expertise from analytical biochemists, toxicologists, pharmacologists, clinicians, statisticians, regulatory professionals, clinical research professionals and market access specialists. Getting it right the first time is a daunting challenge. Delays, technical setbacks and disjointed execution can be costly, even fatal, to the journey. A well-designed, global strategy is the surest route to efficient development and commercial success.

PAREXEL has a heritage of complex product development and, as a partner to industry since the beginning of the biosimilars era, we have the expertise to navigate the complexities—scientific, clinical, legal and regulatory—developers face on the biosimilar journey. PAREXEL can help you identify risks and find the most efficient path to market.
The first step on the biosimilar journey and the foundation of all subsequent development is to demonstrate physicochemical and functional similarity between the proposed biosimilar and the appropriate licensed reference product(s). Yet the exact requirements for establishing similarity may differ from one regulatory system, or country, to another.

The EU has led the way in establishing an abbreviated approval pathway for what it terms “similar biological medicinal products.” With its March 6, 2015, approval of the first-ever US biosimilar product, Sandoz’s Zarxio (a biosimilar of Amgen Inc.’s Neupogen), the FDA has now begun setting precedents of its own. For example, in its Zarxio review, the FDA introduced a four-tier critical quality attribute (CQA) classification system that ranks the importance of similarity attributes from “very high” to “very low” with regard to their potential impact on potency, purity, and safety (see table on the next page for a sampling of the issues).

Whatever the regulatory system, all biosimilar developers must establish adequate similarity or risk failure. The complexity of this undertaking increases as one moves from simple, non-glycosylated proteins to complex, highly post-translationally modified proteins such as mAbs.
### Key Quality Attributes for Demonstration of Analytical Similarity

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Key Similarity Considerations</th>
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<tbody>
<tr>
<td>Product-related</td>
<td>Percent protein content, pH, osmolarity, qualitative and quantitative composition of key excipients</td>
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<tr>
<td>Structure of active substance</td>
<td>Primary structure must match reference product, differences in higher order structure (folding) in theory may impact pharmacokinetics, efficacy, immunogenicity, and safety; and any differences will need to be justified robustly as having low or no impact</td>
</tr>
<tr>
<td>Isoforms of active substance</td>
<td>Differences in isoform distribution such as side chain variants, glycosylation and N or C terminal truncation or modification must be robustly justified; differences are assumed to be significant until proven otherwise</td>
</tr>
<tr>
<td>Impurities</td>
<td>Process-related impurities (host cell proteins, trace solvents and leachables) may not impact biologic activity, but may adversely affect the immunogenicity profile; product-related impurities – depending on % content, activity level, and potential for undesirable activity/immunogenicity – have a variable impact, from very low to very high</td>
</tr>
<tr>
<td>Biological activity</td>
<td>Potency, receptor binding and, for mAbs, both target (antigen) and Fc binding</td>
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</tbody>
</table>

**Always very high**  **At least high criticality**  **Variable criticality**

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**AT PAREXEL, WE PARTNER WITH CLIENTS TO:**

- Define a risk-based, stepwise “totality of evidence” approach
- Help establish an unambiguous understanding of the structure-function relationships in order to decrease clinical data requirements and support data extrapolation across multiple indications in line with the reference product approval
- Advise on how to probe potential differences with multiple complementary analytical techniques and exploit different molecular properties to maximize the ability to detect differences and determine whether they can be justified
- Provide guidance on a production strategy that limits the impact of process changes during development

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**BIOSIMILAR JOURNEY STEP 2
STREAMLINE CLINICAL DEVELOPMENT**

Ideally, if structural and functional data demonstrate similarity with a high degree of certainty, biosimilars would only need to be tested in a limited clinical program involving pharmacokinetic (PK) and pharmacodynamic (PD) endpoints in healthy volunteers (if ethical), possibly supplemented by immunogenicity testing in a target patient population. In reality, most biosimilar products developed today are required to undergo therapeutic equivalence trials in patient populations. As the field evolves, the use of PK/PD and exposure-response data (including from modeling) may substantially abbreviate some biosimilar clinical development programs.

For now, the key to planning and executing a rapidly-moving biosimilar clinical development program is to avoid mistakes that compromise timelines. PAREXEL is one of the world’s largest and most experienced clinical research service providers with hands-on global experience in support of many different
biosimilar development campaigns. As such we have the infrastructure, harmonized processes, subject matter experts and advanced technologies to help clients achieve results under tight deadlines.

To date, we have:

- Designed highly streamlined biosimilar clinical development programs accepted by key regulatory agencies
- Expeditiously conducted phase 1 biosimilar PK/PD trials in more than 2,000 healthy volunteers (HVs) since 2009
- Managed more than 30 comparative phase 3 biosimilar therapeutic equivalence trials—spanning rheumatology, oncology and hematology—in more than 4,000 patients at nearly 600 sites
- Achieved excellent recruitment times in a hypercompetitive clinical development environment (e.g., we have recruited 120 HVs in 4 weeks for a mAb PK/PD study and enrolled 600 rheumatoid arthritis patients for a comparative phase 3 trial within 2 months)

### BIOSIMILAR mAb CLINICAL TRIAL REQUIREMENTS DIFFER BY COUNTRY/REGION

<table>
<thead>
<tr>
<th></th>
<th>REPRESENTATIVE EARLY PHASE/BRIDGING TRIALS</th>
<th>REPRESENTATIVE THERAPEUTIC EQUIVALENCE TRIALS</th>
<th>Extension/switch study may be required for US</th>
</tr>
</thead>
<tbody>
<tr>
<td>EU</td>
<td>Three-way PK bridging study in 120+ healthy volunteers (HVs) comparing biosimilar with EU-approved and US-licensed reference product</td>
<td>Single global trial of approximately 600-800 patients – can incorporate patients from China and other regions, but must use EU-approved or US-licensed reference product</td>
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<tr>
<td>US</td>
<td></td>
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<tr>
<td>JAPAN</td>
<td>Comparative PK bridging study in ~100 patients</td>
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<tr>
<td>CHINA</td>
<td>PK equivalence study in Chinese HVs</td>
<td>Study in at least 600 patients in China. Extended CT approval period.</td>
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<tr>
<td>INDIA, RUSSIA, BRAZIL, ETC.</td>
<td>PK/PD in ~60 subjects but can use EU/US study above</td>
<td>Study in 100-200 local patients [e.g., India, Russia]</td>
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REGULATORY DEFINITIONS OF BIOSIMILARITY: EMA VERSUS FDA

European CHMP:
• Similar (no difference in amino acid sequence).
• "It is not expected that the quality attributes will be identical. Minor structural differences may be acceptable but must be justified."
• "Differences in impurity profiles should be justified."

US Food and Drug Administration:
• “Highly similar.”
• “Notwithstanding minor difference in clinically inactive components.”
• “No clinically meaningful differences in terms of the safety, purity and potency.”

BIOSIMILAR JOURNEY STEP 3

NAVIGATE REGULATORY COMPLEXITY

As regulatory agencies across the globe grapple to ensure that biosimilars attain the required level of similarity to their reference product(s), they are generating an ever-expanding maze of guidelines, requirements and standards. A globally-relevant and shrewd regulatory strategy is vital to a streamlined and successful biosimilars development program.

From concept to marketing approval, developers need to expertly address each of the following with respect to every regulatory environment in which they intend to operate:

• Agency interactions (key topics/supporting positions)
• Pre-submission meetings
• Compelling messaging throughout the dossier
• Responses to agency questions

• Presentation at advisory committee meetings and hearings
• Setting and complying with post-approval commitments

Complicating matters further, regulations and requirements will continue to evolve.

PAREXEL has supported four EU-approved biosimilar development plans and marketing authorization applications (MAAs), with a fifth in progress. We have a proven regulatory track record in both the US and Europe and we maintain significant expert presence in other major regions and countries including Japan, China, Taiwan, Russia, Ukraine, Turkey and Latin America.

Because we create more than 1,000 regulatory documents a year worldwide, PAREXEL has unrivaled expertise in preparing INDs/CTAs, NDAs/BLAs/MAAs, and agency briefing books. We bring all of these resources to the table for our biosimilar clients, as we did recently when we filed an MAA within 25 days of receiving the final clinical report.
Even with a perfectly executed development program, biosimilar products can face intense competition in the marketplace.

Access hurdles facing biosimilars:

• EU and US product launches currently require the same kind of marketing and educational support as for a branded drug; this will continue for the foreseeable future.

• The biosimilars marketplace is evolving rapidly, with new players entering and industry partnerships taking shape, complicating planning.

• In order to leverage their portfolio and market position to defend against single biosimilar competitors, companies use bundling and rebates.

• The concept of biosimilarity is poorly understood by prescribers, who have grown to expect clinical data to support their prescribing and are therefore not familiar with the "totality of evidence".

• How the FDA eventually defines "interchangeability", pivotal for enabling less expensive biosimilars to substitute for branded biologics, is a question mark over the nascent US market.

• Uncertainty over nonproprietary naming standards could mean biosimilars in the US have a different name than the originator product (for example, the FDA opted to assign the name "filgrastim-sndz" to Zarxio, rather than just filgrastim). This differs from generic drug naming conventions used worldwide— as well as from current EU practice for biosimilars—and could hamper uptake.

Despite these significant access challenges, developers can help cost-conscious healthcare payers champion biosimilar products that have a sound basis for safety and efficacy. The obstacles and uncertainties marking the first decade of the industry will inevitably give way to new challenges and new opportunities.
WHEREVER YOUR JOURNEY TAKES YOU, WE’RE CLOSE BY.