

Biosimilar Development Clinical Investigator Considerations

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Biosimilar products are not new in the pharmaceutical industry. However, the pending expiration of numerous therapeutic monoclonal antibody patents highlights the importance of biosimilar development as a cost-saving option for patients and health care systems worldwide and as a business opportunity for drug developers.

Biosimilars are also called follow-on biologics, similar biological medicinal products and similar biotherapeutic products. These products come to market after extensive development programs to provide evidence of the similarity of the product to the innovator molecule. The task of establishing this similarity encompasses technical, preclinical and clinical evaluations. This similarity analysis may allow data studied in one indication to be extrapolated to another indication not specifically studied in the biosimilar clinical development program.

Key Aspects of Product Comparability

Quality Assessments

(demonstration of similarity of a biosimilar and innovator)

Biochemical properties

Physicochemical properties

Biological activity

Immunochemical properties

Impurities

Manufacturing Process

Should be optimized to minimize differences between the biosimilar and innovator

Nonclinical Assessments

(dependent on quality comparability exercise)

Pharmaco-toxicological assessment of biosimilar

Clinical Assessments

(comparative study utilizing the innovator)

Pharmacokinetic studies

Pharmacodynamic studies

Pharmacokinetic/pharmacodynamic studies

Efficacy and safety studies

Immunogenicity assessments

World Health Organization:

Similar biotherapeutic product

A biotherapeutic product, which is similar in terms of quality, safety and efficacy to an already licensed reference biotherapeutic product.

Several different terms have been used for biosimilars, including follow-on biologics, similar biological medicinal products, and similar biotherapeutic products. The term "biosimilar" is used in this document.

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Regulatory advice for biosimilar development, including guidance from the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA), continues to rapidly evolve. The EMA was the first regulatory agency to release detailed guidance, beginning with a general guidance on the topic in 2005 (EMA, 2005). This document is being supplemented by a series of class-specific guidances. A draft of the next in the series, on monoclonal antibodies, was published in 2010 with finalization expected in 2011. Covering duration, sample size and appropriate endpoints, this set of guidances provides an EMA roadmap for biosimilar development programs.

Because the U.S. FDA approves biologics through a different statutory pathway than small molecule drugs, the regulatory pathway for biosimilars has been slower to emerge. The first guidelines from the U.S. FDA are anticipated in 2011.

As regulatory agencies clarify the pathways to approval of biosimilars, many organizations are seizing the opportunity to produce innovative yet similar alternatives to important biological medicines that are nearing the end of patent protection. Numerous development programs are underway, creating acute demand for investigators and patients to participate in trials of biosimilar products.

Selected Top Biologic Therapies with Expired Patents or Impending Expiration*

Drug Class	Drug Name	Generic Name	Indication(s)	Approved
Hormone	Humulin®	human insulin	Diabetes	1982
	Humatrope®	somatropin	Growth failure	1987
	Epogen®	epoetin alfa	Anemia	1989
	Procrit®	epoetin alfa	Anemia	1990
Vaccine	Engerix-B®	hepatitis B vaccine	Immunization	1989
Enzyme	Cerezyme®	imiglucerase	Gaucher's disease	1991
Cytokine	Intron A®	interferon alfa-2b	Cancer, infection	1986
	Neupogen®	filgrastim	Neutropenia	1991
Clotting factor	NovoSeven®	recombinant factor VII	Hemophilia	1992
Monoclonal antibody	Rituxan®	rituximab	Cancer, RA, vasculitis	1997
	Remicade®	infliximab	Psoriasis, RA, other immune	1998
	Herceptin®	trastuzumab	Cancer	1998
Novel synthetic protein	Enbrel®	etanercept	RA, psoriasis, other immune	1998

RA = rheumatoid arthritis

*Patents for the product expire after 20 years; application typically occurs during the drug development stage.

Data from Frank RG, "Regulation of follow-on biologics," *N Engl J Med* (2007;357(9), 841-843); Dudzinski DM, Kesselheim AS, "Scientific and legal viability of follow-on protein drugs," *N Engl J Med* (2008; 358(8), 843-849); "Top 500 prescription drugs," *Med Ad News* (2004, 2007, 2009), www.pharmalive.com.

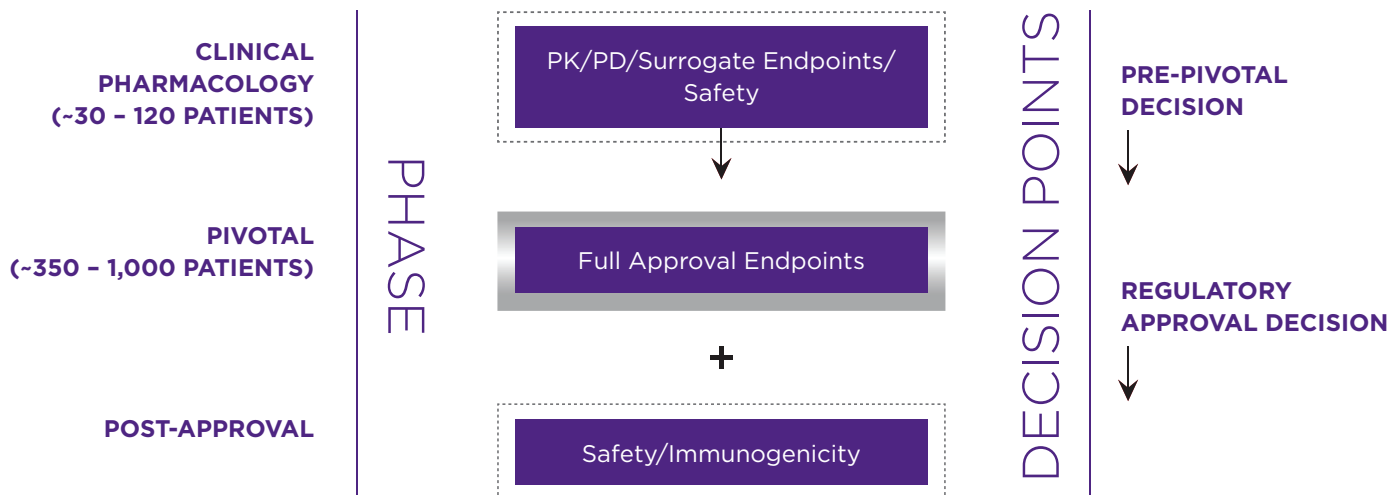
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Biosimilar Development Program Design: Meeting the Challenges

For biosimilars, the requirements of the research program are more extensive than those of a small-molecule generic. The program must still demonstrate pharmacokinetic equivalence to the innovator. The design of pharmacokinetic studies for monoclonal antibodies may be complicated by the long half-lives and the need for continued dosing. These features may make biosimilars ill-suited to the usual cross-over design of a bioequivalence trial, thus increasing sample sizes needed.

After demonstrating pharmacokinetic and pharmacodynamic equivalence, biosimilars, with few exceptions, require an extended clinical research program. Since the efficacy of the innovator product is known, Phase II trials are not required, but sufficient safety and efficacy data must be generated to demonstrate the similarity of the product to the innovator.

BIOSIMILAR DECISION POINTS AND DEVELOPMENT PLAN



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Clinical trial programs for biosimilars include active comparators, which are generally the innovator product approved for use in the particular country. This requirement can contribute to the complexity of trial design, but it offers a compensating advantage for patients by providing access to often-expensive life-changing treatments. Furthermore, the therapeutic options made available in a biosimilar trial – an established active comparator and an agent designed to be similar to it – may encourage investigator involvement.

The biosimilar trial program must establish similarity in both efficacy and safety, but the program may be streamlined: novel trial designs, such as adaptive trials and Bayesian hierarchical models, may maximize the efficiency of the program by reducing the number of subjects required (Berry et al, 2011). Nevertheless, the demand for clinical trial investigators will remain high, and an educated biosimilar community will be an important factor in the success of biosimilars, both in the development and eventual marketing of these important medicinal products.

Efficacy endpoints may differ from those in innovator trials. In oncology, for example, overall survival is a common primary endpoint. For a biosimilar trial of a cancer therapeutic, the focus is on similarity to the innovator rather than overall patient benefit. Surrogate endpoints, selected in consultation with regulatory authorities and guidances, may be the most appropriate. Overall response rates, progression-free survival and even novel endpoints such as a waterfall plot of tumor response have been suggested (EMA, 2010).

Because the process for producing a biologic product is complex, subtle changes can occur at any stage of manufacturing that may alter the safety profile (including immunogenicity) of the product. Therefore, most biosimilar products are expected to be approved only with a post-marketing commitment to monitor safety.

Strict regulatory compliance will help to maximize the chances for approval. The sponsor should obtain guidance from all countries where the biosimilar product will be marketed.

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Conclusion

Biologic therapies have improved health care for chronic diseases, including cancer, yet high cost has limited the accessibility of these valuable therapies. Patent expirations prepare the way for sponsors to develop biosimilar products that, because of their similarity to proven products, have a high probability of success.

Investigators who are interested in participating in biosimilar development trials should contact **PPD Biosimilar Product Development Services** at ***biosimilarworkgroup@ppdi.com*** for additional information.

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