



Development and Testing Services for the Commercialization of Biosimilars

Biopharmaceuticals have grown tremendously in the last decade, with the global biologics market estimated to be \$53 billion (excluding vaccines) and constituting nine percent of the global pharmaceutical market. As patent protection for successfully marketed biopharmaceuticals expires, the door opens for the development of biosimilar products. The established safety and efficacy of a marketed product greatly reduces development risk for a biosimilar. The prospect of high market revenue, supported by high cost-of-development barriers to new competitive drugs, motivates many biosimilar product developers. Multiple biosimilars have entered European and other markets where regulatory approval processes are in effect, and the FDA has released draft guidance documents for the development of biosimilars in the US.

Biosimilar programs performed at Charles River

- Cytokines
- Growth factors
- Monoclonal antibodies
- Hormones

Major Issues in Developing Biosimilars

Biosimilars, like the reference biologic products, are complex protein structures that are difficult to characterize. Therefore, a development program consisting of analytical and bioanalytical assays, pharmacology and/or toxicology studies in animals as well as clinical trials are conducted to show that biosimilars are highly similar to the reference biological product. Production processes are highly complex, expensive and can be difficult to control. However, control is essential to product uniformity, hence the assertions that, for biologics, “the process is the product”, and that follow-on products cannot be regarded as “generic.”

Biosimilars are biological products sufficiently similar to a reference product to gain regulatory approval to be marketed for treatment of at least one health condition for which the reference product has market approval. Regulatory authorities regard the biosimilar and reference products as having no clinically meaningful differences in terms of safety, purity and potency. Biosimilars are intended to be used at the same dose and administered by the same route as the reference product.

Capabilities to Support Development and Commercialization of Biosimilars

Biopharmaceutical Testing and Manufacturing Services

Charles River delivers client-focused solutions for the specific testing and manufacturing requirements of your biosimilars. Services include cell bank creation and storage, safety testing, process evaluation for viral clearance, cell bank characterization, product characterization, stability, equivalence and product release testing.

Cell Bank Creation and Storage

- Expertise in the creation of master and working cell banks
- GMP-compliant programs, conducted according to FDA Points to Consider and ICH Q5D guidelines

Cell Bank and Raw Material Safety Testing

- Detection of adventitious agents including:
 - *In vivo* and *in vitro* detection of general viral contamination
 - Specific assays for human, simian, bovine, porcine and murine viruses
 - Hamster and mouse antibody production test
- Detection of retroviral contamination using electron microscopy, XC plaque assay, S+L-focus assay, reverse transcriptase assays and co-cultivation assay
- Detection of microbial contamination

Product Characterization

- GMP-compliant lot release and stability testing services to ensure the quality and consistency of the manufactured product
- Meet FDA and ICH guidelines at several stages of the regulatory process

Testing to Demonstrate Biosimilarity

Charles River also supports biosimilar comparability testing. Showing biosimilarity is a multi-faceted comparative exercise that includes quality preclinical and clinical assessments. Charles River provides the following in support of clients' biosimilar and biobetter product development.

- Bioassays
- Mass Spectrometry
- Toxicology Studies

Bioassays

By directly measuring the potency of a fully conformed protein, bioassays are central and critical for product development and manufacturing to ensure continued quality, safety and efficacy of biopharmaceutical products. Charles River has experience in developing, transferring, validating and conducting *in vitro* and *in vivo* bioassays to GMP for the release of marketed product and to GLP for products in the earlier stages of development. For nearly 10 years, Charles River has been responsible for testing every batch of many marketed biological products for European and US release using bioassays.

- Development, transfer, validation and use of appropriate methods to confirm the identity, purity, potency and quantity of biological products
- Meet ICH requirements

Lot Release Testing

- Testing to ensure that no part of the manufacturing process has failed and affected the finished product
- Testing of unprocessed bulk harvest, purified bulk and final fill
- GMP lot release of products for global markets, including EU-based testing for EU release

Stability Testing

- Characterization tests required to demonstrate stability and integrity of the drug substance and product in a variety of formulations including solution, suspension, creams, tablets, capsules, sterile ampoules, lyophilized powders and pre-filled syringes
- ICH stability conditions required for product registration in the EU, US and Japan

Equivalence Studies

- Study Design
- Implementation of studies required to demonstrate equivalence following changes to the production process or to meet generic manufacturing requirements

Mass Spectrometry

Through a partnership with Protagen—a GMP-certified specialist in the characterization of proteins—Charles River offers expanded protein characterization services. Protagen's extensive mass spectrometry capabilities allow Charles River to offer services covering the entire range of protein analytics, including biosimilar comparability studies. These services include protein quantification, protein primary structure, glycosylation, protein modification and protein impurity analysis. Protagen's services are conducted in compliance with ICH Q6B guidelines and analyses can be carried out to full GMP standards.

Toxicology Studies

Charles River's scientific and regulatory consultants can assist with the design of appropriate preclinical development programs to meet worldwide regulatory requirements. The types of preclinical studies conducted to support approval for the reference product, as well as subsequent technological advances, should be considered when designing a preclinical program for a biosimilar.

Once programs are designed, the studies are conducted by industry-accredited technicians, study directors and senior scientists located at several GLP-compliant facilities in the US, Canada and UK. The general approach and scope of preclinical services needed for biosimilars is the same as those needed for new biological entities. These services include, but are not necessarily limited to, analytical (dose formulation analysis), bioanalytical (toxicokinetics and immunogenicity), immunohistochemistry (e.g., tissue cross reactivity) and immunology (e.g., flow cytometry and other biomarkers as appropriate). In many cases, the toxicology studies for biosimilars will need to be conducted in large animal models, but in some cases rodents might also be appropriate. Charles River is an industry leader in these service areas with over 20 years of experience in biologics development.

- Investigations range from single-dose to chronic studies
- Large animal and rodent studies
- Infusion and other parenteral routes
- Rapid, managed IND-enabling preclinical programs
- Lab services capabilities for pharmacokinetics/toxicokinetics and immunogenicity testing, immunochemistry, immunohistochemistry and immunotoxicology

Quality Assurance, Regulatory Consulting and Program Management

Charles River has extensive experience providing guidance on expectations, GLP, GCP and GMP. We offer regulatory consulting and program management with a focus on efficient communication through our client managers, providing a single point of contact for multi-study/site programs.

- Experience with GLP, GCP, GCPv and GMP
- Toxicology consultancy and expert reviews, data review and gap analysis
- Single point of contact for multi-study programs

Representative Regulatory Guidelines

The regulatory status of biosimilars varies among regions, with Europe being the leader. In 2005, the European Medicines Agency (EMA) adopted an overarching biosimilar guideline, which was followed by product-specific guidelines. For example, guidelines for biosimilar products containing somatropin, erythropoietin and granulocyte colony-stimulating factor have been adopted. In 2010, EMA released a draft guideline addressing biosimilar monoclonal antibodies and concept papers on follicle stimulating hormone and interferon beta. Similar to the EMA, Canadian and Japanese regulatory authorities and the World Health Organization (WHO) have released biosimilar guidelines. In contrast, a legal pathway for biosimilars development was not created in the US until March, 2010. In February, 2012, the FDA published the series of draft guidance documents to define their recommendations for biosimilars development.

Representative Regulatory Guidelines

• Europe

- Similar biological medicinal product, CHMP/437/04, 2005
- Guidance on similar medicinal products containing somatropin, CHMP/94528/05, 2006
- Guidance on biosimilar medicinal products containing recombinant granulocyte colony-stimulating factor, CHMP/31329/05, 2006
- Guideline on non-clinical and clinical development of similar biological medicinal products containing recombinant erythropoietin (Revision), EMEA/CHMP/BMWP/301636/08, 2010
- Additional EMA biosimilar guidelines and concept papers can be found in the regulatory section of the EMA website: <http://www.ema.europa.eu>

• US

- Scientific Considerations in Demonstrating Biosimilarity to a Reference Product, 2012
- Quality Considerations in Demonstrating Biosimilarity to a Reference Protein Product, 2012
- Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009, 2012

- **Canada:** Guidance for sponsors, information and submission requirements for subsequent entry biologics (SEBs), 2010
- **Japan:** Guideline for ensuring quality, safety and efficacy of biosimilar products, PFSB/ELD Notification No. 0304007, 2009
- **WHO:** Guidelines on evaluation of similar biotherapeutic products (SBPs), WHO/BS/09, 2110, 2009
- **Possible Regulatory Strategy for US and EU**
 - Develop a CMC, preclinical and clinical program based on EMA guidelines
 - Hold a pre-IND/pre-BLA meeting with the FDA, specifying that the request is for a biosimilar (also referred to as a 351(k)) program, and/or seek input from appropriate EU regulatory authority.

Technical Considerations and Capabilities to Support Biosimilars Development

Charles River's involvement in registration studies for new drug products, including lot release testing and preclinical pharmacology and toxicology, extends over 20 years. The experience gained with the specialized testing of biological products compared to small molecules means that Charles River understands the complexities involved and can apply this knowledge to developing testing programs for biosimilars.