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Development and Testing Services for the Commercialization of Biosimilars

Biosimilars, like their reference biologic products, are complex protein structures that are difficult to characterize. Therefore, a development program is conducted to show that biosimilars are highly similar to the reference biological product. This program typically consists of analytical and bioanalytical assays, pharmacology and/or toxicology studies in animals, as well as clinical trials. 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."

Biologics 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, similarity assessment and product release testing.

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 bioassays, mass spectrometry and toxicology stuides in support of clients' biosimilar and biobetter product development.

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 meet or exceed the appropriate regulatory standards, from early development stages through to release of marketed product. For over 10 years, Charles River has been responsible for testing every batch of many marketed biological products for European and US release using bioassays.

Through a partnership with Protagen®, a Good Manufacturing Practice (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.

Biosimilar programs performed at Charles River

- Cytokines
- Growth factors
- Monoclonal antibodies (mAbs)
- Hormones
- Enzymes

Services

- Biopharmaceutical testing and manufacturing services
- Testing to demonstrate biosimilarity
  - Toxicology
  - Bioassays
  - Mass spectrometry
  - Immunogenicity
  - Pharmacokinetic and pharmacodynamic assay
- Quality assurance, regulatory consulting & program management

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These services include protein quantification, protein primary structure, glycosylation, protein modification and protein impurity analysis. Protagen's services are conducted in compliance with International Conference on Harmonisation (ICH) Q6B guidelines and analyses can be carried out to GMP standards.

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.

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 US Food and Drug Administration (FDA) published a series of draft guidance documents to define their recommendations for biosimilar development.

Technical Considerations and Capabilities to Support Biosimilar 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.

Quality Assurance, Regulatory Consulting and Program Management

Charles River has extensive experience providing guidance on expectations of Good Laboratory Practice (GLP), Good Clinical Practice (GCP) and Good Manufacturing Practice (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.

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

Biosimilar Experience	
Generic name	Indication
Rituximab	Rheumatoid arthritis Non-Hodgkin's Lymphoma
Infliximab	Crohn's Disease Rheumatoid arthritis
Trastuzumab	Breast Cancer
Adalimumab	Rheumatoid arthritis
Erythropoietin	Anemia
Pegfilgastrim	Neutropenia
Filgastrim	Neutropenia
Natalizumab	Multiple Sclerosis
Teriparatide	Osteoporosis
Forsteo	Human Parathyroid Hormone
Adalimumab	Auto-immune disease

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