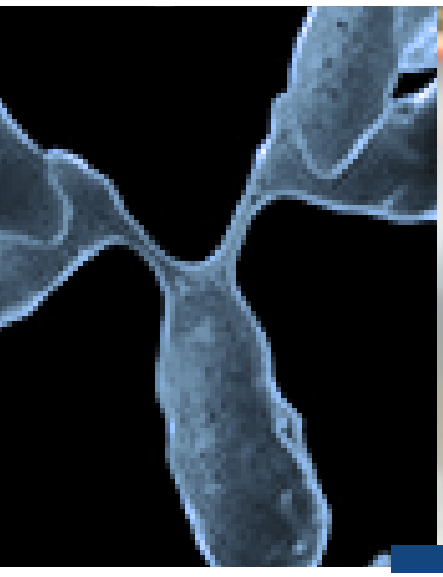
charles river



Biosimilar Development

Services

- Expression system optimization/clone selection
- GMP testing and manufacturing support
- Originator product characterization
- Biosimilarity assessment
- Reference standard characterization
- Lot release
- Stability testing
- Quality assurance, regulatory consulting and program management

As a true end-to-end CRO, Charles River offers the multidisciplinary expertise and capabilities to support our clients' development of a diverse range of biosimilar drugs. Combining years of experience in the development of biologic products with a deep knowledge of regulatory requirements, we have created a comprehensive program to support our clients' biosimilar development programs from GMP facilities for performing originator characterization and comparability to *in vivo* preclinical studies and preclinical and clinical sample analysis through final product lot release.

Expression System Optimization/Clone Selection

Charles River offers assays for expression-level quantification and confirmation of product sequence and post translational modifications (PTMs). The methods we use depend on the critical quality attributes of the biosimilar product, and may include chemical, structural and functional assays.

GMP Testing and Manufacturing Services

We deliver client-focused solutions for the specific testing and manufacturing requirements of biosimilar products. Services include cell bank creation and storage, biosafety testing, process evaluation for viral clearance, cell bank characterization, product characterization, potency/activity assays, stability and product release testing.

Originator Product Characterization

This is typically performed concurrent with the development of the biosimilar expressing cell line(s). As specialists in advanced analytics, we use a variety of techniques to thoroughly establish the quality attributes of the originator/reference product. Our methods include modes of chromatography, electrophoresis, mass spectrometry and biophysical techniques.

EVERY STEP OF THE WAY

Testing to Demonstrate Biosimilarity

Demonstrating biosimilarity is a multi-faceted exercise that includes preclinical and clinical assessments. We provide unstressed and forced degradation analytical comparability programs between originators and biosimilars that include analytical, mass spectrometry and biophysical methods, along with bioassays and toxicology studies.

Unstressed Comparability Programs

We routinely conduct comprehensive side-by-side analytical comparison studies between the biosimilar and originator products by assessing purity, impurities, aggregation, sequence confirmation, disulfide mapping, PTM mapping and quantification by LC-MS/MS and secondary and tertiary structure analysis by a combination of biophysical techniques, including circular dichroism, Fourier-transform infrared spectroscopies, intrinsic and extrinsic fluorescence and differential scanning calorimetry.

Forced Degradation Comparability Programs

Charles River also supports side-by-side forced degradation programs. Stress conditions include thermal, pH, oxidation, agitation, freeze/thaw and UV/visible photolysis. We then apply the appropriate analytical methods for the characterization of the stress material and identify/quantify impurities generated by the forced degradation.

Bioassays

Functional characterization goes beyond chemical properties to show the impact of drugs in cellular systems. By directly measuring the potency of a fully conformed protein, bioassays are central and critical for product development, comparability studies and release testing to ensure continued quality, safety and efficacy of biopharmaceutical products. Our skilled team can develop, transfer, validate and conduct *in vitro* and *in vivo* bioassays that reflect the mechanism of action of therapeutic compounds. These assays meet or exceed the appropriate regulatory standards, from early development stages through to release of marketed product.

Toxicology

In vivo pharmacokinetic or toxicology studies are often required to compare the exposure and toxicity of the reference product and the biosimilar. Offering comprehensive, integrated services, Charles River draws upon the expertise of the many toxicologists in our safety assessment group to perform these studies and meet the regulatory requirements for submission.

Nonclinical and clinical pharmacokinetics, immunogenicity and pharmacodynamics

We have extensive experience in developing and validating assays for nonclinical and clinical bioanalysis, immunogenicity and biomarkers of interest for biosimilars programs. Often, clients choose to partner with Charles River early in the development phase to develop these assays to support nonclinical *in vivo* pharmacokinetics or toxicology studies and continue their relationship with our analytical experts throughout their clinical program. This helps to ensure that all clinical trials meet applicable worldwide regulatory requirements.

Reference Standard Characterization

Essential for the analysis of both originator biologics and biosimilars, reference standard characterization requires a broad spectrum of analytical methods and instrumentation for comprehensive assessment of drug purity, identity, potency and stability. We employ a multitude of techniques in the analysis of biosimilar reference standards. These include, but are not limited to, mass spectrometry for molecular weight, peptide mapping and glycan profiling, chromatography methods for amino acid analysis and extinction coefficient determination, biophysical characterization by CD, AUC, and intrinsic/extrinsic fluorescence, cIEF to determine charge profiling and isoelectric point and general analytical methods for pH, osmolality and western blot analysis.

Lot Release

Following the in-depth characterization of the biosimilar, a panel of tests must be selected to establish the quality control specification for the drug substance and finished product for use in batch release and stability testing. This panel includes tests for purity, strength, potency and safety (impurities and contaminants). Each test must undergo qualification and validation, depending on the stage of product development. Charles River provides release testing services for bulk drug substances and clinical and marketed products in the European Union (EU), United States (US) and other regulatory-distinct markets, and can act as a single site for global release testing needs.

Stability Testing

Biosimilar programs require comprehensive stability studies that emphasize the comparability with the reference product early in their development. Our team can perform these stability studies to evaluate biosimilar products under various environmental conditions over a specific timeframe, recommend suitable storage and shipment conditions for drug substances and products, and determine the appropriate shelf life or retest period. Because diverse views are held by international regulators, we recommend that full method validation to GMP standards is conducted prior to the commencement of these studies to avoid program delays.

Quality Assurance, Regulatory Consulting and Program Management

In 2005, the European Medicines Agency (EMA) adopted overarching biosimilar guidelines, which were followed by product-specific guidelines. For example, guidelines for biosimilar products containing somatropin, GCSF, monoclonal antibodies and interferon beta have been adopted. Other regulatory authorities have followed with their own guidelines, notably the World Health Organization (WHO) in 2009 and the US FDA, finalized in 2015.

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 with former FDA personnel and program management with a focus on efficient communication through our client managers, providing a single point of contact for multi-study/site programs.

As the authorities continue to refine their biosimilar and other guidance documents, we continue to monitor regulatory developments globally and ensure our programs meet not just finalized guidelines, but also developing expectations.

Charles River's Biosimilar Experience	
Class	Molecule
Hormones	Teriparatide, Parathyroid hormone (PTH), Erythropoietin (EPO)
Cytokines	Filgrastim and Pegfilgrastim, Molgramostim
mAbs	Rituximab, Trastuzumab, Cetuximab, Nivolumab, Pembrolizumab, Bevacizumab, Ranibizumab, Natalizumab, Infliximab, Adalimumab
Other	Glatiramer acetate, Etanercept

charles river

askcharlesriver@criver.com • www.criver.com