
BUILDING A BIOLOGIC
charles river

BUILDING A BIOLOGIC

A single cell. Insignificant on its own, perhaps. But when engineered with the correct framework that single cell may be capable of becoming a factory of lifesaving material. With the right support, this individual entity will grow from hundreds to millions to billions of cells, churning out a protein that might one day change the way we prevent, treat, or even cure ailments that affect the ones we love.

At Charles River, we see the cell for the valuable building block that it is. As your partner in drug development, we can help you build your biologic through services that support you every step of the way, from cell banking, rapid microbiology, and microbial identification solutions through to impurity, potency, biosafety, and viral clearance services.

Bringing therapies to the patients who need them is a complex but satisfying journey. Let us be your guide.

CELL BANKING

You have spent years creating a foundation: discovering the correct target, inserting genetic code in just the right place, and modifying cell lines to produce your biologic with precision. Now that you have a solid foundation, you are ready to move forward with creating your master and working cell banks.

Charles River is a partner you can trust to ensure the quality, consistency, and integrity of your cell banks. With more than 15 years of experience in GMP cell bank manufacturing, our skilled team provides a smooth and successful outcome for your manufacturing campaign.

- More than 1,500 cell banks produced for our clients
- Mammalian cell lines, insect cell lines, stem cells
- Aerobic and anaerobic microorganisms

BUILD YOUR BIOLOGIC

Your cell bank is the critical starting point of your production process. By establishing a stable cell bank, you'll have a standardized cell line free of contamination and genetic drift, providing years of reliable cell performance in your process.

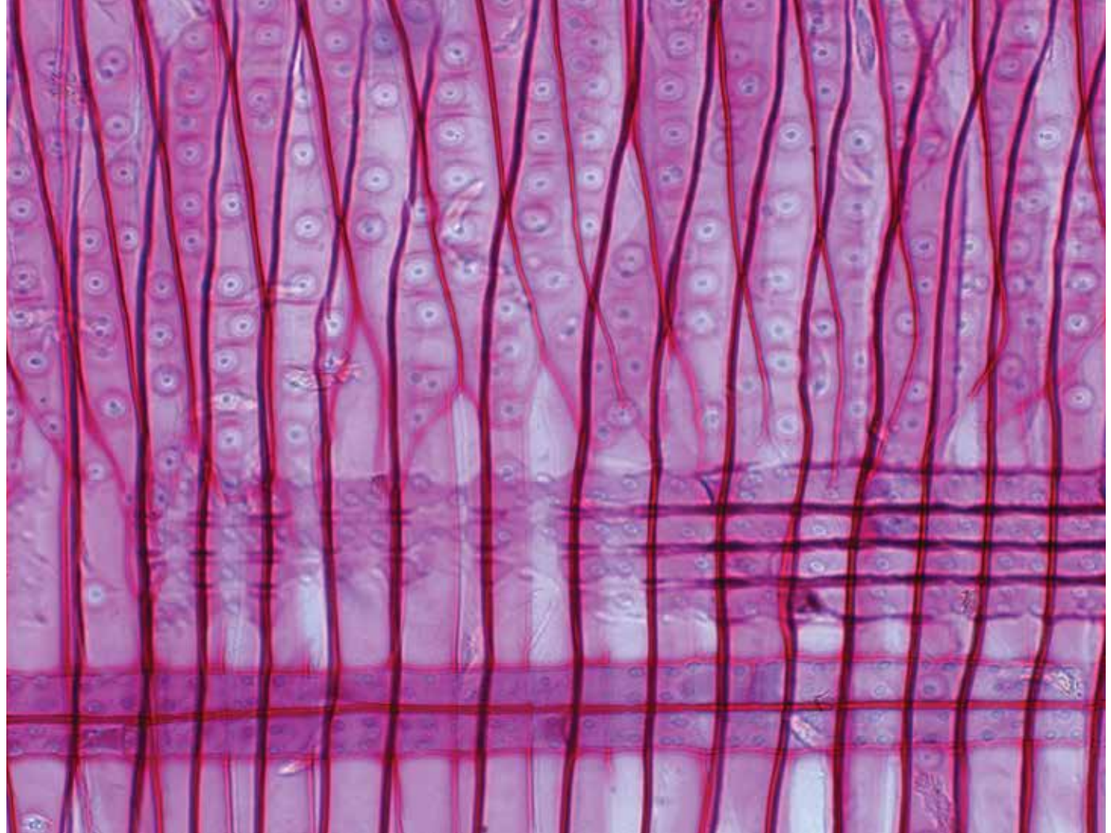
— Nicole Posey,
Manager, Manufacturing Services

CELL LINE CHARACTERIZATION

The characterization of your cell banks is an integral part of ensuring the integrity of your biologic years down the road. You need a service provider who can assist you in determining the most appropriate testing program for characterization studies to provide the information you need to make critical decisions moving forward.

Though many aspects of testing are similar across the industry, our team works to understand your needs. With a mastery of regulatory requirements and a comprehensive portfolio of testing services, we tailor project designs that suit the unique qualities of your cell line.

- Approximately 225 cell banks characterized annually for our clients
- Only AAALAC-accredited facility for *in vivo* biosafety testing in the United States
- Only GLP TEM provider in the United States



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To ensure that you are working with a cell line fulfilling all regulatory requirements, it is important to test your MCB, WCB, EOPC, or PPCB according to the international guidelines. For this, Charles River offers the expertise to analyze identity, genetic stability, and potential contaminations by viruses, mycoplasma, or bacteria.

— Dr. Ilja Quadt,
Supervisor, Biosafety & Bioassay Services

POTENCY

The complex infrastructure of biologics leads to specialized methods being needed to determine their potency. *In vivo* and *in vitro* bioassays begin during the early development phase of a biologic with method development efforts and extend throughout its whole life cycle including lot release testing during commercialization efforts.

The intricate nature of large molecules can make it difficult to perform bioassays and achieve reliable results. Charles River delivers consistency with extensive experience in the establishment, validation, and conduct of routine bioassays to GMP standards. We provide comprehensive coverage, offering both *in vitro* and *in vivo* bioassays for a variety of biologically active molecules. Our experience includes over:

- 750 *in vitro* bioassays performed each year
- 2,100 *in vivo* bioassays performed each year
- 1,000 lot release bioassay tests performed each year

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Bioactivity assays should reflect the mechanism of action of a biologic in the patients and use state of the art technologies to ensure reliable results.

— Dr. Ulrike Herbrand,
Scientific Director,
Global *In Vitro* Bioassays

CONTAMINATION TESTING

Safety considerations are part of any well-planned construction project. From preclinical lots through routine bulk harvest testing of clinical and marketed batches, contamination testing helps ensure the safety of your biologic before it is released for use in animals and humans.

Customers have access to a portfolio of compendia assays for the detection of mycoplasma and bacterial contaminants, as well as *in vivo*, *in vitro*, and biochemical viral detection assays. Our experts can design and develop the appropriate testing plan for your biologic, with a selection of available and customized assays that suit your specific needs and ensure the absence of adventitious agents.

- More than 20,000 reports sent each year from sites across the globe
- Support for more than 200 licensed products
- Fast Track testing for urgently needed results

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Testing for adventitious agents, coupled with a thorough risk assessment, is the keystone of biosafety.

— Brian Ruvolo,
Director, Biologics Testing Services

IMPURITIES

Residual host cell protein (HCP) evaluation is a key building block in the preclinical stage of development. Generic assays may be used in preclinical and early clinical stages for impurity detection, but once Phase III studies are reached, a validated assay specific for your product needs to be in place. Regulatory agencies expect manufacturers to develop a thorough understanding about the performance of the downstream purification process with respect to the removal of host cell proteins and other impurities.

Charles River has the capabilities to support testing of all process stages for impurities such as residual Protein A, DNA, Tween, endotoxin, and host cell proteins.

- In-house polyclonal antibody production from SPF animals
- ELISA method development for HCP detection
- Identification and quantitation of individual HCPs using mass spectrometry
- HCP-GAPexSM-targeted enhancement of antigen coverage by ELISA
- Multiple offerings for residual DNA assays

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Host cell proteins are an inevitable impurity of biopharmaceuticals. Even after multiple sophisticated purification steps, HCPs remain or co-purify with the drug substance. To protect patients from adverse effects, such as immunogenicity, powerful and reliable analytical tools are required to monitor such impurities during the manufacturing process and in final release testing.

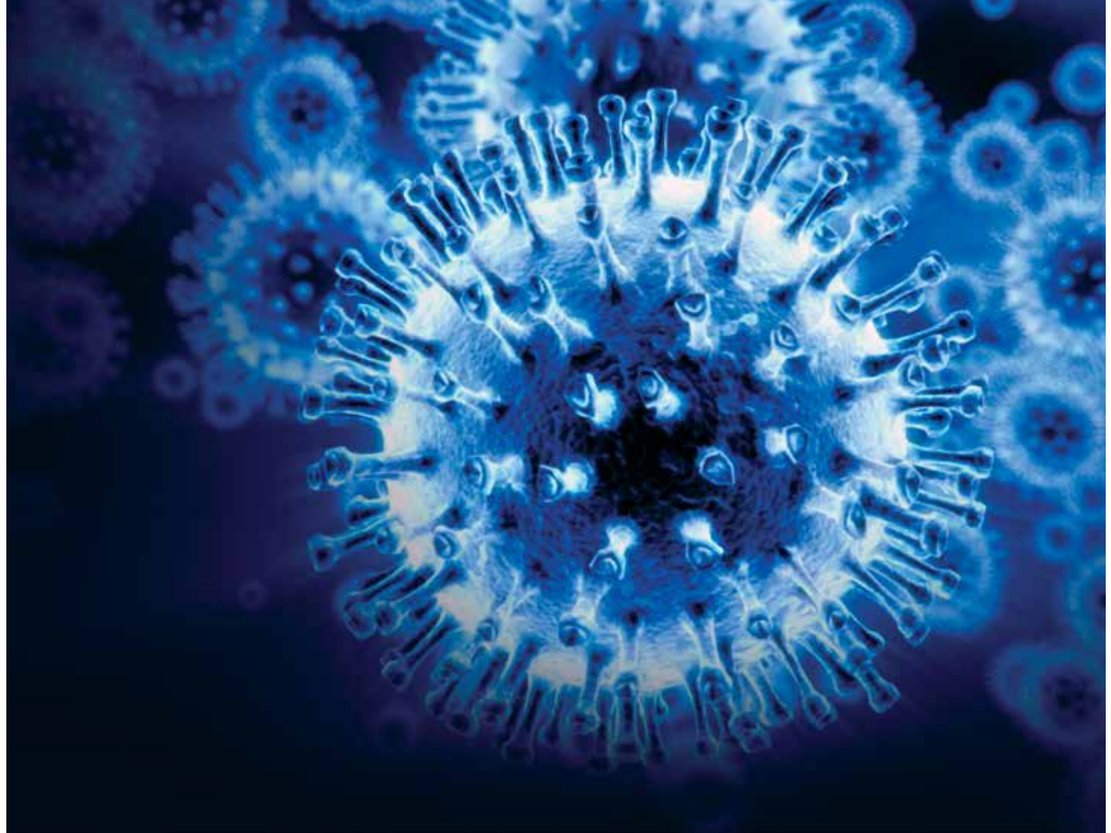
— Dr. Olaf Stamm,
MDRA Senior Specialist, Biologics
Testing Solutions Europe & Asia

VIRAL CLEARANCE

Viral clearance studies are important for reinforcing the structure of your production and purification processes by demonstrating their virus removal and inactivation potential. Initial studies must be included in your IND filing, while larger studies begin later in Phase III of your clinical studies for your NDA/BLA filing.

Using a customized approach, we can provide technical advice and regulatory support to ensure that a successful and cost-effective program is established and reports are generated to meet your deadlines.

- More than 2,100 viral/TSE clearance studies performed
- ICH Q5A, WHO, Europe, US, and Japan regulatory compliance
- Facilities in the United States and Europe



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The efficacy of the first three virus safety barriers for virus entry into a biopharmaceutical product – knowledge, careful material sourcing, and a detailed testing program – cannot compete with the level of virus safety brought into the product with the fourth barrier, a viral clearance program.

— Dr. Horst Ruppach,
Global Manager of Viral Clearance and
Global Coordinator of Virology

LOT RELEASE TESTING

Your biologic is built, but as a viable product, its life has just begun. Lot release testing ensures your product's ongoing safety and efficacy profile, verifying a match with specifications stated in the regulatory paperwork. Moreover, indications that arise in the future may be added to the biologics repertoire, necessitating approval and additions to your license.

Charles River provides release testing services for bulk drug substances and clinical and marketed products and can act as a single site for your global release testing. We are committed to successful long-term relationships with our clients and work closely with operational staff, offering flexibility to meet clients' manufacturing schedules.

- Full specification release testing of more than 500 batches of 20+ final products each year
- Involvement in approximately 20% of all batch releases of biological products sold in Europe
- Product release support for US, EU-27, UK, and other regulatory-distinct markets

BUILD YOUR BIOLOGIC

Manufacturing schedules may not always go as planned. It is important to have flexibility in your lot release testing laboratory to help your supply chain run smoothly and ensure that your biologic gets to the patients who depend on it.

— Niall Dinwoodie,
BSc MSc CChem MRSC, Senior Director,
Global Analytical Services

STABILITY

The quality of your biologic is assured, but how long will it retain those characteristics? Stability studies play a critical role in all stages of the registration process, starting with your initial IND submission. Later, stability testing is a key component in the clinical phase of development to be included in your NDA/BLA application, in post-marketing commitments, and in support of any future process changes.

Charles River performs stability studies for biopharmaceutical products and drug substances at all stages of the registration process. Over the past 20 years, we have designed, managed, and executed stability testing programs to support early development, formal submission studies per the ICH guidelines, and commitment studies for the continued marketing of existing drug products.

- Included on multiple product licenses approved by the FDA, USDA, and EMA authorities
- ICH, sub-ambient, and specialized storage conditions available
- Consultation services and troubleshooting expertise

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Stability testing is an important component of product development, and is used to establish appropriate shelf life and storage conditions for client products, both after manufacture and also at various stages in the manufacturing process. Charles River is set up to develop and perform a range of stability-indicating test methods and store samples under controlled conditions for the duration of stability studies.

— Ian Parsons, PhD
Director, Analytical Development

RIGHTSOURCE℠

As rewarding as the end result may be, bringing your biologic to market involves a substantial investment of time and money. As you strive to improve efficiencies and reduce costs, it is wise to evaluate strategic sourcing initiatives, including closer collaboration with contractors.

Our RightSource℠ program removes the challenges of externalizing biologics testing by providing customized options that allow you to maintain as much or as little control over your in-house resources, capital assets, and facilities that you consider strategic and cost-efficient. We work with you to evaluate your QC testing programs and select the best-suited, most affordable mix of insourcing and outsourcing options.

- Complimentary introductory consultation
- Dedicated, experienced project management staff
- Maintained high visibility of testing activities for clients

BUILD YOUR BIOLOGIC

Companies struggle with finding a balance between performing work internally and outsourcing it to contract research organizations. It is important to them to keep control of the testing and timelines, but they may not have the technical skills or funding to support it. A mixed insourcing/outsourcing program, such as RightSource℠, allows clients to maintain the visibility they want but offers them an option to introduce cost savings and focus on their core competencies.

— Zane Honnold
Director of Global Sales

SPECIALTY BIOLOGICS

The building blocks for specialty biologics such as vaccines and biosimilars share some similarities, but also have many unique attributes compared to other biologics. As an experienced contract laboratory partner, Charles River can guide you along the unique developmental pathways of these products.

VACCINES

Charles River can help you expedite your vaccine development program by providing you with manufacturing support for early-phase clinical trials through lot release programs for commercial products.

SERVICES

- Manufacturing
  - » cGMP cell banking
  - » virus seed and pilot scale virus preparation
- Cell Substrate/Virus Characterization and Safety Testing
- Potency Assays
- Vaccine Challenge Studies
- Stability Testing

BUILD YOUR BIOLOGIC

Charles River has consistently and effectively supported the vaccine development industry for decades with a unique range of products and related services. Working with our global network of scientific, technical, and regulatory experts provides vaccine developers with the right expertise early in the vaccine development process to boost productivity, efficiency, and profitability.

BIOSIMILARS

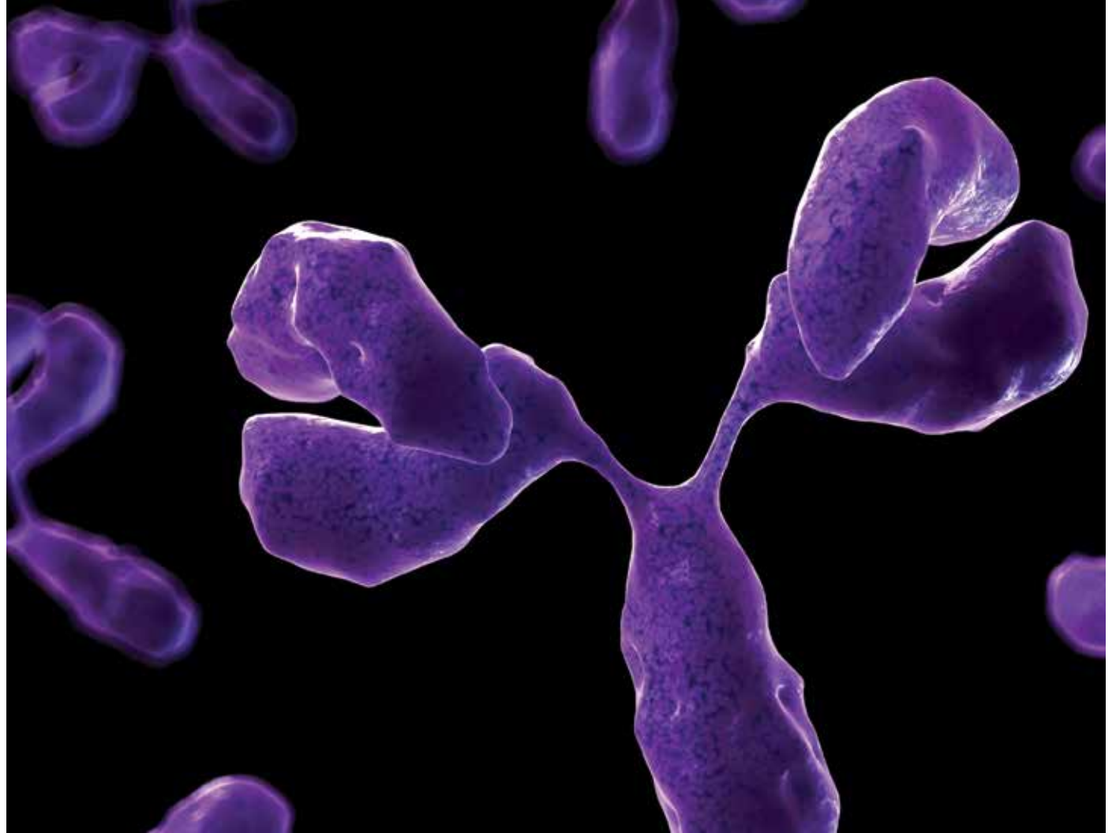
Biosimilar production processes are complex, expensive, and can be difficult to control, so it is essential to partner with professionals who can perform the full development program while providing the control essential for product uniformity. Charles River delivers client-focused solutions for the specific testing and manufacturing requirements of your biosimilar.

MANUFACTURING AND TESTING SERVICES

- Cell Bank Creation and Storage
- Cell Bank and Raw Material Safety Testing
- Potency Testing
- Lot Release Testing
- Stability Testing
- *In vitro* Assessment of Immunogenicity: ADA, mAb detection assay, cell-based immunogenicity

SERVICES TO DEMONSTRATE BIOSIMILARITY

- Design and execute comparability studies to demonstrate biosimilarity
- Mass spectrometry characterization for primary sequence confirmation and PTMs
- Biophysical characterization for secondary and tertiary structural analysis
- Bioassays (*in vitro* and *in vivo*): binding assay, ADCC, CDC, apoptosis, other relevant mode of action (MoA) assays



BUILD YOUR BIOLOGIC

Our experience working with biologics across the drug development continuum, together with our scientific and regulatory expertise, makes Charles River an ideal partner for your biosimilar development.

LET US HELP BUILD YOUR BIOLOGIC

Your biologic has an impact on the health and wellness of those we love. Whether you are in the early stages of building your biologic or are ready to take it to market, Charles River is an experienced partner, capable of supporting your development every step of the way.

BUILD YOUR BIOLOGIC

With the most comprehensive biologics testing portfolio in the industry, Charles River offers protocols to meet global regulatory requirements. From biosafety testing and impurity detection to potency determination and lot release programs, our team of scientists and project managers ensures that the most appropriate methods are used for your product.

FACILITIES AND CAPABILITIES

	Pennsylvania, USA	Massachusetts, USA	United Kingdom	Ireland	Germany	France
Abnormal Toxicity/General Safety		•	•	•		•
Antisera Production				•		•
Biophysical Characterization Studies		•				
Biosafety Testing	•	•	•	•	•	
Bulk Harvest and End-of-Production Testing	•	•	•	•	•	
Cell Banking (GMP and R&D)	•					
Cell Line Characterization	•	•	•	•	•	
Chromatography and Electrophoretic Methods	•	•	•	•		
Contamination and Impurity Testing (e.g., mycoplasma, adventitious viruses, residual DNA, etc.)	•		•	•	•	
Custom Method Development	•	•	•	•	•	•
Cytotoxicity				•		
Disinfectant Efficacy Testing	•			•	•	
Endotoxin Testing	•		•	•	•	
Environmental Monitoring Services	•			•		
Formulation Development		•				
Genetic Stability Testing	•		•		•	
Glycosylation/Glycan Characterization		•				
Host Cell Protein Determination	•	•			•	
Identification of Bacterial Isolates	•			•		
Immunopotency/Immunogenicity Testing				•		
In Vitro Potency/Bioassays		•	•		•	
In Vivo Biosafety Testing		•	•	•		
In Vivo MAP, RAP, and HAP Testing		•	•	•		
In Vivo Potency/Bioassays		•	•	•		
Lot and Final Drug Product Release	•	•	•	•	•	
Mass Spectrometry Services		•				
Master and Working Virus Seed Production	•					
Microbial Limits/Bioburden Testing	•			•		
Monocyte Activation Testing (MAT)				•		
Murine Toxicology Testing				•		
Preservative Efficacy Testing				•		
Process- and Product-Related Residuals		•				
Process Characterization (Resin Cycling)	•				•	
Protein Characterization	•	•	•	•	•	
Pyrogen Testing				•		•
Reference Standard Characterization		•				
Spore Count Verification				•		
Stability Testing	•	•	•	•	•	
Sterility Testing	•			•		
Vaccine Challenge Studies				•		
Vaccine Safety Assays	•	•	•	•	•	
Viral Clearance Studies	•				•	
Water Testing Services	•			•		

For links to global regulatory documents governing biologics development and manufacturing, please visit our Biologics Regulatory Library at **www.criver.com/regulatory**

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www.criver.com