

***In Vivo* Biosafety Testing Services Sponsor Information Packet**

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Overview

Bioproducts that result from biopharmaceutical production are required to be tested *in vivo* with animal models. This approach allows a bioproduct's individual components to be examined and their potential toxicities on target tissues to be determined. The resulting safety and toxicity data is valuable, as it will impact initial clinical trial parameters. This animal biodistribution data aids researchers in making safety decisions, such as estimating initial human dose and the dose escalation scheme, as well as identifying problems with the product, prior to clinical trials.

The *In Vivo* Biosafety (IVB) Testing Services is a specialized technical group of Charles River Laboratories that performs preclinical research studies according to FDA Good Laboratory Practice (GLP) regulations and product release/efficacy tests which conform to the United States Pharmacopoeia Compendium (USPc) requirements. These studies and test methods comply with the most stringent international standards for the use of laboratory animal models to demonstrate the safety of medical products. Scientific studies performed by the IVB Staff are used to establish the safety and efficacy data base for regulatory master files submitted in the United States and foreign countries. Release and efficacy tests are performed on licensed biomedical products to obtain final approval and release of individual production lots of biomaterials.

At Charles River Laboratories, available services include Mouse/Rat/Hamster Antibody Production (MAP/RAP/HAP) assays to screen for and identify murine viral contaminants in biological specimens, as cell lines derived from rodent tissues and cell cultures require testing prior to cell banking or use in *in vivo* studies. Additionally, we offer both the Inapparent Virus Assay and the General Safety Test. The Inapparent Virus Assay screens for extraneous viruses known to not cause any cytopathic or other cytological effects in cell culture, while the General Safety Test determines the safety and efficacy of a biomedical product in support of investigational and new drug filings. Detailed information for each test can be found below, in the *Available Services* section.

Available Services*

** Please refer to Page 10 for pricing*

Mouse, Rat, and Hamster Antibody Production (MAP/RAP/HAP) Tests

The Mouse/Rat/Hamster Antibody Production (MAP/RAP/HAP) tests are immunologically-based protocols designed to simultaneously detect and identify viral contaminants in biological specimens, as cell lines derived from rodent tissues and cell cultures require this testing prior to cell banking and cell characterization. The Antibody Production tests are generally performed under FDA Good Laboratory Practice (GLP) conditions, but can be completed in a non-GLP manner for a “quick and dirty” approach before full-scale testing.

The animals are inoculated by multiple routes with a test article and held in isolation for four weeks. Serum samples are collected and serologically tested for the virus-specific antibody by way of the enzyme-linked immunosorbent assay (ELISA); detection of specific antibodies equates to the test article having been exposed to a virus. The turnaround for MAP/RAP/HAP testing is approximately 6 to 8 weeks. Please refer to Page 8 for pricing and a list of agents targeted for each Antibody Production test.

With the growth of the biotechnology industry, biologics derived from rodent tissues and cell culture are being administered to people more frequently, so these products must be tested to show that they are free of harmful extraneous rodent viruses. One example is Lymphocytic Choriomeningitis Virus (LCMV). This virus is a zoonotic agent that can cause disease in people, and is one of the viruses that we regularly test for in the Mouse Antibody Production (MAP) serology panel.

MAP/RAP/HAP Sample Submission Information

To submit test articles for MAP/RAP/HAP testing, 5×10^6 cells/mL is recommended for completion of the test panel. Cells should be diluted 1:1 in supernatant or 1:4 in ascites; no additional media is required. A total volume of 4.0mL is needed to perform the MAP test panel, whereas 2.5mL are required for the RAP and HAP tests; all samples should be free of bacteria. Samples should be shipped in a manner that is best suited for the sample being testing; please contact Technical Services to discuss the shipping of your specific sample.

Samples submitted for IVB must be accompanied by a completed Test Article Submission Form and shipped, with a yellow Research Animal Diagnostic Services Submission Label affixed to the package, to the following address:

Charles River Laboratories
In Vivo Biosafety Testing Services
251 Ballardvale Street
Wilmington, MA 01887

Please check the box next to “Animal Testing”, and check the testing type (either “GLP” or “Non-GLP”). Also, please circle the storage temperature. Upon receipt, samples are stored in dedicated storage units according to client specifications.

To obtain a Test Article Submission Form and a yellow shipping label, please call Technical Services at 1-800-338-9680 or e-mail comments@crl.com.

Inapparent Virus Assay

The Inapparent Virus Assay tests for extraneous viruses that do not cause any damage, disorder or destruction of cells in culture. The detection of these inapparent viruses is particularly useful in vaccine studies and is a required step during novel drug development; test articles must meet the criteria of this assay before proceeding further towards clinical studies. The Inapparent Virus Assay is considered our most complex test, and is performed under GLP conditions. This assay includes a 28 day period in which several species (guinea pigs, embryonated chicken eggs, adult and suckling mice) are inoculated with a test article through various routes, and are then monitored daily for the prescribed observation period. A summary report is generally issued within 10 days of completion of the in-life phase of the study. Unlike the Antibody Production test, which is based on serologic results, the Inapparent Virus Assay results are based on test animal clinical well-being and survival rates. If necessary, the standard protocols for the Inapparent Virus Assay can be customized by an amendment, as long as the relevant support data and documentation is provided by the sponsor.

Inapparent Virus Assay Sample Submission Information

A total test article volume of 41mL is required to complete the Inapparent Virus Assay. Any sample submitted for this test must be free of bacteria. Samples should be shipped in a manner that is best suited for the sample being testing. To ensure the best results, please contact Technical Services to

discuss your sample type and shipping conditions. Upon receipt, samples are stored in dedicated storage units according to client specifications.

Samples submitted for IVB must be accompanied by a completed Test Article Submission Form and shipped, with a yellow Research Animal Diagnostic Services Submission Label affixed to the package, to the following address:

Charles River Laboratories
In Vivo Biosafety Testing Services
251 Ballardvale Street
Wilmington, MA 01887

Please check the box next to “Animal Testing”, and check the testing type (either “GLP” or “Non-GLP”). Also, please circle the storage temperature. Upon receipt, samples are stored in dedicated storage units according to client specifications.

To obtain a Test Article Submission Form and a yellow shipping label, please call Technical Services at 1-800-338-9680 or e-mail comments@crl.com.

General Safety Test

The General Safety Test aids in determining the safety and efficacy of a biomedical product in support of investigational and new drug filings; this *in vivo* testing is a critical role and is required by United States Pharmacopeia (USP) federal policy for vaccine development. The General Safety Test is a 7 day experiment performed under GLP conditions. Like the Inapparent Virus Assay, the General Safety Test is a survival study; 100% of the inoculated guinea pigs and mice must not only survive the observation period, but must also gain weight and not exhibit any clinical signs of illness. If necessary, the standard protocols for the General Safety Test can be customized by an amendment, as long as the relevant support data and documentation is provided by the sponsor.

General Safety Test Sample Submission Information

A total test article volume of 11mL is required to complete the General Safety Test. The sample should be shipped in its final commercial container. All samples submitted for the General Safety Test should be free of bacteria. Please contact Technical Services to discuss the submission of your specific test article. Upon receipt, samples are stored in dedicated storage units according to client specifications.

Samples submitted for IVB must be accompanied by a completed Test Article Submission Form and shipped, with a yellow Diagnostic Services Submission Label affixed to the package, to the following address:

Charles River Laboratories
In Vivo Biosafety Testing Services
251 Ballardvale Street
Wilmington, MA 01887

Please check the box next to “Animal Testing”, and check the testing type (either “GLP” or “Non-GLP”). Also, please circle the storage temperature. Upon receipt, samples are stored in dedicated storage units according to client specifications.

To obtain a Test Article Submission Form and a yellow shipping label, please call Technical Services at 1-800-338-9680 or e-mail comments@crl.com.

IVB Testing at Charles River Laboratories

Scientific/Technical Staff

IVB testing is managed by several experienced scientists, who are responsible for overseeing the development of protocols, standard operating procedures and testing methods that will fulfill the scientific objectives of each research study or test. The Scientific Director collaborates with the department manager and the highly experienced Study Directors, who supervise the daily activities of the staff of certified IVB Technologists. Technologists are certified prior to performing any procedures and are re-certified annually to ensure their ability to work independently. Procedures conform to accepted methods for research and testing as determined by multiple levels of scientific and Sponsor review. Each animal model used in research or testing is carefully selected to achieve reproducibility of results and clearly demonstrate the objectives of the study or test. Whenever possible, animal models and methods of research or testing are verified with regulatory agencies and evaluated for reproducibility by comparative testing.

Facilities

There are two specialized laboratories in the IVB facility. One such area is the Centralized Facility, 2,100 square feet broken up into seven rooms for animal housing and laboratory space. The second is a dedicated Biological Containment Laboratory (BCL) with isolation capabilities. The facilities are environmentally controlled and have back-up emergency power for critical equipment and functions. All animals in the Centralized Facility are housed in sterile Microisolator[®] cages on either static or ventilated cage racks. All care and use procedures are performed in HEPA filtered biosafety hoods. Animals in the BCL unit are housed continuously in Microisolator[®] cages inside isolation units with glove ports. All instrumentation and equipment is maintained, calibrated, and certified annually according to a preventive maintenance program and outside service contracts.

Animal Care and Use Program

The IVB program of animal care and use is closely monitored by Charles River's Institutional Care and Use Committee (IACUC) for conformity with The Guide for the Care and Use of Laboratory Animals and the "Animal Welfare Act." The program is subject to routine site visits by regulatory agencies, sponsors, and peer review accrediting agencies. Studies and tests performed by the IVB group are monitored regularly by an independent Quality Assurance (QA) group, which certifies the collection of data, documentation methods, reporting of data and the issuance of the final study or test report. The IVB group, as part of Charles River Laboratories Research Animal Diagnostic Services, performs studies in compliance with pertinent federal regulations:

- Accredited by the Association for Assessment and Accreditation of Laboratory Animal Care – International (File 000125)
- Possesses an Assurance of Compliance with the NIH Office of Laboratory Animal Welfare (A3863-01)
- Registered with the United States Department of Agriculture (USDA, 14-R-0144)
- Licensed to handle biohazardous agents by the USDA

IVB Research and Testing

The IVB group specializes in testing biomedical products for the presence of inapparent viruses. Tests can be used to distinguish production media origin or cell associated viruses through comparative *in vitro* and *in vivo* testing methods. These methods include the Antibody Production test in mice, hamsters or rats, the Inapparent Virus Assay, and the General Safety Test.

The IVB team has performed more than 400 research studies and certified release/efficacy tests annually using standardized rodent models and embryonated chicken eggs. Each animal model selected is based upon established FDA, USPc, or other scientifically referenced animal models. Protocols are written and performed in compliance with GLP guidelines based upon an extensive list of written Standard Operating Procedures and pre-established customized study report forms.

The IVB group has 10 standardized research protocols to establish a safety and efficacy database for a wide variety of biomedical products. Recently, our IVB personnel have implemented a comprehensive group of safety protocols to establish master files for a wide range of vaccine preparations. Vaccine preparations for SARS, small pox, Dengue, West Nile Virus, and other pathogenic viruses have been established.

The Quality Assurance (QA) department at Charles River plays an important role in IVB research and testing when performed under GLP conditions. A member of the QA group must watch and approve at least one phase of every single study. Additionally, the Final Report, which includes a Quality Assurance Statement with dates and phases of these inspections, is audited by our QA staff. The members of our QA department also conduct internal audits to ensure that the IVB laboratory follows the proper procedures as outlined in federal regulations.

Charles River Laboratories Support Services

Data Management

Sponsors submitting samples for IVB will have the option to use our data management system, the Internet Laboratory Information Management System (ILIMS). ILIMS was created to meet the data management needs of our sponsors as well as aid in the efficient design and implementation of our laboratory QC Programs, providing real-time results on-line. Offered free of charge to all Charles River sponsors, this browser-based application was designed to be a user-friendly, secure, and confidential QC program management tool that allows the user the flexibility of utilizing as much of the systems features as necessary.

Data confidentiality is paramount to us at Charles River Laboratories. ILIMS was designed with safety in mind, utilizing the latest in internet-security technology. The system is equipped with firewalls, secure socket layers (SSL) for data encryption, and password protection to limit access to applications and your information to authorized personnel. In addition, each user is assigned a role that controls their ability to view and edit information.

On-line reporting allows the sponsor to receive results the instant they been approved and cleared for reporting. Additionally, for non-GLP studies, the sponsor can choose to receive results via e-mail, fax, phone, or mail, or as unaudited results for GLP studies. Results reported into ILIMS are automatically archived.

In the case of GLP studies, an original hard copy final report, including the ILIMS results report, is always shipped to the client directly, with the required Study Director signatures and QA statement; a faxed copy may be sent for client convenience as a secondary method of result transmission. Although sponsors may receive these results by way of email through ILIMS, the email documents will not suffice to support an IND filing with the FDA.

Laboratory Animal Model Selection

Charles River Laboratories commercially produces a wide variety of scientifically accepted rodent models which are commonly used for safety or efficacy studies. All rodent models are free of enzootic diseases, which can adversely affect the biological data in a rodent study. Charles River can also provide surgical animal models for special types of studies or tests. In some circumstances, special strains of laboratory rodents need to be established for research or testing purposes. In these instances, Charles River can establish a colony in its Transgenic Services group, or acquire the strain of animal from an outside source.

Research Animal Diagnostic Services

Charles River Research Animal Diagnostic Services offers assays and products designed for comprehensive, accurate, and reliable laboratory animal testing. Managed by highly-qualified professional staff, Research Animal Diagnostic Services assists customers in monitoring and analyzing the health and genetics of research models used in their research facilities. Research Animal Diagnostic Services operates under the same system of QA monitoring and certification as its IVB laboratory. Routine laboratory services and tested species include:

<i>Testing Services</i>	<i>Species</i>
<ul style="list-style-type: none"> • Serology Testing and Reagents • Pathology, Histology and Parasitology • Infectious Disease PCR Testing • Microbiology and Environmental Monitoring • <i>In Vivo</i> Biosafety Testing • Plasma Biomarker Analysis 	<ul style="list-style-type: none"> • Mouse • Rat • Hamster • Gerbil • Guinea Pig • Rabbit

Technical Writing Capabilities

The professional staff members in the IVB group are trained to create technical literature including research protocols, standard operating procedures, study reports, and other documents for proposed studies. The staff members work with the IACUC, QA, and other scientific information sources to generate internal working documents in an expeditious time frame. This process is facilitated by two computer information systems – Master Control and Internet Laboratory Information Management System (ILIMS), which allow documentation to be assembled.

Scientific Consulting

The IVB group consults actively with potential sponsors to establish the scientific basis for achieving the research or testing objectives. Additionally, IVB team members have access to input from other Charles River scientific groups, which are staffed by highly-trained and experienced scientists and veterinarians. Specialized scientific advisory groups are also consulted when unique scientific

aspects of a project are anticipated. All consulting is performed under a confidentiality agreement between Charles River and the sponsor.

Frequently Asked Questions (FAQs)

- ***Who do I contact to receive additional information and to receive a cost estimate for my study?***

Please contact our friendly representatives at Charles River Laboratories Technical Services by calling 1-800-338-9680 or e-mailing comments@crl.com.

- ***What is the confidentiality policy?***

All information provided by a sponsor is treated as proprietary and may be covered by a standard confidentiality agreement when required. Each study or test is given a unique tracking code which precludes sponsor or Test Article information from appearing on cage cards, or other working records. All proprietary information is restricted to the study or test file documents under the control of the Study Directors, affiliated scientific staff, or QA Auditors.

- ***What are the responsibilities of the Sponsor prior to testing?***

Sponsors are obligated to sign protocols and provide sufficient descriptive information on the Test and Control Articles to allow Charles River to meet regulatory requirements as well as independently assess any potential hazard to IVB personnel. Additionally, sponsors are responsible for the quality of any Test or Control Articles so that untoward reactions in animal models can be prevented. Typically, Test and Control Articles must be sterile by an acceptable method and non-pyrogenic by Limulus Amebocyte Lysate assay. Other pre-study or pre-test requirements may be necessary depending upon scientific information gathered in behalf of project.

- ***My research is not performed in the United States. Can I still send my samples to Charles River's IVB team in Wilmington, MA?***

Yes, we can still perform your IVB testing. We have established protocols that satisfy United States, European, and Japanese regulations. If we do not have a protocol that suits your needs, we can work with you and follow the direction of your regulating body to establish the proper protocols.

Do you have questions or require additional information? Please contact Charles River's Technical Services:

251 Ballardvale Street
Wilmington, MA 01887
Telephone: 1.800.338.9680
E-mail: comments@crl.com.



Pricing for Available Services

<i>In Vivo</i> Biosafety Test	2007 Pricing per GLP Test
Mouse Antibody Production (MAP) Test, 19 Viruses *	1,825.00
Mouse Antibody Production (MAP) Test with LCMV Challenge *	1,895.00
Rat Antibody Production (RAP) *	1,825.00
Hamster Antibody Production (HAP) *	1,825.00
Inapparent Virus Assay	Upon Request**
General Safety Testing	Upon Request**

* Please refer to the table below for agents tested. Antibody Production tests can also be performed non-GLP.

** Please contact Technical Services at 1-800-338-9880 for a study-specific cost estimate or discuss **customized study design**.

Agents Targeted in the Antibody Production Tests

Agent Name	Abbrev.	MAP	RAP	HAP
Sendai virus	SEND	X	X	X
Pneumonia virus of mice	PVM	X	X	X
Minute virus of mice	MVM	X	X	X
Mouse polio virus	GDVII	X	X	X
Reovirus Type 3	REO	X	X	X
Lymphocytic choriomeningitis virus	LCMV	X	X	X
Hantaan virus	HANT	X	X	X
Mouse hepatitis virus	MHV	X		
Rodent parvovirus, Non-Structural Protein 1	PARV NS1	X		X
Mouse Parvovirus	MPV	X		
Epizootic diarrhea of infant mice	EDIM	X		
Mouse pneumonitis virus	K	X		
Ectromelia	ECTRO	X		
Polyoma virus	POLY	X		
Mouse adenovirus	MAV 1 & 2	X	X	
Mouse cytomegalovirus	MCMV	X		
Mouse thymic virus	MTLV	X		
Prospect Hill Virus	PHV	X		
Lactate dehydrogenase virus	LDV	X		
Sialodacryoadenitis virus	SDAV		X	
Kilham's Rat virus	KRV		X	X
Toolan's H-1 virus	H-1		X	X
Rat parvovirus	RPV		X	
Simian virus 5	SV-5			X