



Placing Preclinical GLP Studies in China: Questions and Answers to Help You Decide

A White Paper Presented by
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September 8, 2008



Executive Summary

Whereas 10 years ago no one thought about placing GLP-compliant preclinical studies in China, soon every biopharma company preparing an IND will take China into account, where GLP study costs are lower, studies can often start sooner, and access to animal models is easier. Right now, however, with GLP studies in China so new, companies considering China have many questions. For example, “*Can China really meet western GLP standards?*” Answer: Absolutely. The FDA recently accepted a GLP nonhuman primate toxicology study performed at Bridge China. “*Are reports in clear, standard English?*” Yes. “*Is it easy to ship bioanalytical samples from China to the US?*” Answer: Usually, yes, but shipping samples for certain species requires a special permit and careful planning to avoid delaying your schedule. As the first company to offer western-level GLP-compliant preclinical study services in China, Bridge Laboratories receives these questions and many others every day. To help you consider your China options from an informed perspective, this white paper contains our answers to the questions we receive most often.



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A New Day Dawns in Preclinical Research

You have probably heard of “*The World Is Flat: A Brief History of the Twenty-First Century*,” the bestselling book by *New York Times* journalist Thomas Friedman. The title summarizes Friedman’s book’s thesis that a world economy is emerging with new players—particularly China and India—competing on equal, flat footing with the established competition from America, Western Europe, and Japan.

For GLP-compliant preclinical services, China is beginning to flatten the competitive landscape. China promises to become a force within the pharmaceutical industry, in fact. This can mostly be attributed to China’s lower labor costs. In the development parks of Shanghai, almost every major pharmaceutical company in the world now has a corporate location.

Foreseeing the opportunity for China-based GLP-compliant preclinical services, several years ago Bridge Laboratories, which is headquartered in Gaithersburg, Maryland, began planning a preclinical services laboratory located in Beijing’s Zhongguancun Life Science Park. This state-of-the-art Beijing laboratory, the first in China built from the ground up to meet international GLP-compliant standards, opened in 2006 and is now conducting GLP studies for several clients in support of IND submissions to the FDA. Data from one of our studies was recently accepted by the FDA. Competitors following our lead may open GLP-compliant facilities of their own in China beginning around 2009.

As the first company to offer preclinical GLP study services in China, we receive many questions about our services. To help you consider your China options from an informed perspective, here are our answers to the ones we receive most often.



The Questions We're Asked Most

Overview Questions

What are the advantages of outsourcing preclinical GLP studies to Bridge in China?

Studies placed with Bridge in China have 3 advantages over studies in the West:

- Quality of services meet US standards while costs are lower because of reduced labor and animal costs
- Studies can often start sooner
- Fewer constraints on access to animal models

Lower study costs in China owe largely to lower labor costs and, of course, are the primary reason to place studies in China. Depending on how difficult the study is and whose prices are being compared, savings in China are considerable. These savings are especially helpful to small companies concerned with reducing their burn rates and making cost-effective decisions on which compounds to advance in development.

Bridge can place studies in China quickly. In contrast, fairly lengthy delays have occurred in starting studies at several CROs in the United States as their capacity starts to fill up.

Describe Bridge's Beijing facility.

Bridge's GLP-compliant, state-of-the-art 84,000 square-foot preclinical CRO facility is up and running today. Our facility has been AAALAC accredited since 2007 for multiple species. It has 26 animal rooms, is fully staffed, and is conducting studies in support of Western submissions, especially to the FDA. We are also finalizing plans to add another building to the facility with more than 100 animal rooms, and we are discussing dedicated capacity agreements with several large and mid-size pharmaceutical companies.

Is doing business in China different than in the West?

The key difference you should know is that traditional Chinese business culture prefers to build *guanxi*, or personal relationships, before getting onto the business issue at hand. This is much less true in Western business cultures, where transactional arrangements independent of personal relationships are fairly common, certainly in pre-clinical outsourcing.

At Bridge Laboratories, we don't believe it is *your* role to adapt to Chinese culture. It is *our* obligation to adapt to you. So our China lab operates according to Western culture as much as possible, intentionally mirroring our lab culture in Gaithersburg, Maryland. Bridge also understands how important time schedules are to our Western clients, and again, not every lab in China provides this type of

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response and adherence to timelines. Finding the right partner in China is very important.

Even though Bridge China fully embraces Western business culture, we do believe *guanxi* is, in the long run, the most rewarding way to do business in China. We recommend you pay a lot of attention to building relationships in China regardless of the CRO you work with. We follow this advice ourselves. We will make every effort to have you visit, and we will try to build a relationship with you.

What are the challenges unique to China in achieving GLP standards for Tox and Safety studies?

What is *not* a challenge is English. SOPs, protocol, data collection, and reports at Bridge Laboratories in China are in English. Our staff in China communicates in English. The challenge unique to China is the current lack of US board-certified veterinary pathologists located in China for reading slides in large numbers. At Bridge, we solve this problem in two ways. We either ship all slides back to the United States for a board-certified pathologist to read, or, when client timelines demand, we send a board-certified pathologist to China to read the slides.

How are Bridge’s Chinese staff trained?

Senior technical and administrative staff from Gaithersburg have relocated to Beijing to take charge of training our staff. Our senior staff are western trained and have US research experience. Beijing’s junior staff members are graduates of Chinese universities, are fluent in English, and their level of scientific training is extremely high. But because the CRO business is young in China, they generally have less business experience than one might find in the US. To increase their experience quickly, we rotate selected individuals from China to our Gaithersburg facility for further training. In addition, we send Maryland staff to Beijing. We believe you will be extremely pleased with our entire staff if you visit us in Beijing.

What about the quality of non-human primates available in China?

This important question has more to do with non-human primates in general than with non-human primates in China specifically. For example, malaria in non-human primates is an issue in both China and the United States and can certainly interfere with the interpretation of data. Hepatitis is another concern. Bridge uses the same stringent procedures for checking diseases in non-human primates in Beijing and Gaithersburg. Our primates are purpose-bred and screened to eliminate malaria, hepatitis, and any other disease you deem important. Both our facilities maintain IACUCs (Institutional Animal Care and Use Committees) and are accredited by AAALAC International (the Association for Assessment and Accreditation of Laboratory Animal Care). AAALAC accreditation is essential



for any facility in China and assures that Western standards for lab animal care are scrupulously maintained.

Give us your criteria for non-human primates and we will meet them. We welcome the opportunity to talk to you about setting up non-human primate colonies and animal models in either of our facilities.

Regulatory Questions

Has the FDA inspected Bridge China?

Although our Gaithersburg facility has been inspected a number of times by the FDA and USDA (the United States Department of Agriculture), the FDA has not yet inspected our Beijing facility.

Have the FDA and EMEA accepted preclinical GLP studies from Bridge China in support of INDs?

Yes, the FDA recently accepted data from Bridge China for a nonhuman primate GLP toxicology study. Currently, we have several US-based clients that have filed GLP studies with the FDA in support of INDs and several more currently conducting studies that will be submitted to the FDA. For the companies with submissions still under review at the FDA, we have not heard that the FDA has any concern about the studies, which were conducted with rats, dogs, and non-human primates. There has been only one filing in Europe, which was in support of a small clinical study.

We have, so far, 6 clients that inspected us, placed studies with us, and are comfortable with filing their study information with the FDA. If you will inspect our laboratory and decide for yourself whether we meet the highest level of GLP and ICH standards, we believe your concerns will be resolved and relieved.

Have EU, US, or Japanese regulatory authorities accepted long-term animal studies (e.g., subchronic, chronic, reproductive) conducted by Bridge in China?

Currently, the longest-term study submitted by Bridge is a sub-chronic study. We have not submitted a chronic study. At this time, Bridge conducts reproductive teratology studies only in Gaithersburg.

FDA inspectors have taken issue with US-based labs performing GLP and non-GLP studies in the same facility. How does Bridge China handle this problem?

Bridge is committed to appropriate separation of test articles and samples and never conducts non-GLP and GLP studies in the same area in China or Maryland.

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Has your Beijing facility submitted studies to Chinese regulatory agencies? Can they provide Chinese language reports?

We can provide Chinese language reports but have not submitted anything of significance to a Chinese regulatory agency. In anticipation of making submissions to the Chinese State Food and Drug Administration (SFDA), our SOPs are being translated from English into Chinese.

Questions About Placing and Monitoring Studies

How do time zone and language differences affect monitoring studies in China?

We have a designated project management team in our Beijing facility that will work closely with your study team to manage your study timelines and ensure two-way communication. You can also choose to communicate directly with the Study Director. In Beijing, our policy is to be on your time and make phone calls at times appropriate for you. A manager on our staff will be assigned responsibility for maintaining constant communication with you as your study proceeds. Your convenience and confidence in communicating with our Beijing staff are extremely important to us.

Flying time from the east coast of the United States to Beijing is approximately 13 to 15 hours. If you prefer to engage an independent on-site agency to monitor studies for you, several US pharmaceutical companies use China Preclinical Management Services for this purpose (CPMS; <http://www.chinapreclin.com>). CPMS is a spinoff of Cambridge Healthcare Associates.

All SOPs are in English. We use Provantis™, in English, as the data collection system in China. We also use Provantis™ in Gaithersburg. Reports from our China labs are written by our scientific staff and peer-reviewed.

What about intellectual property protection?

No CRO stays in business without protecting intellectual property. So the suggestion made by some that intellectual property may be compromised in China is not true. Our Chinese employees are trained to protect IP. All employees in Beijing sign a non-compete and/or confidentiality agreement when they are hired. We have electronic access control throughout the entire facility, and animal rooms require fingerprint ID to enter. Computers are directly linked to Provantis™, which has no storage capabilities or USB drives. The data generated is directly downloaded on the server, and access to the server for data retrieval requires the authorization of the Study Director and Supervisor. We also have two independent networks within the facility – one used for the lab area and one used for the administrative area.

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Are there special requirements or time constraints for shipping test articles to China or shipping bioanalytical samples from China to the US for specialized testing?

We are not aware of any problems getting test articles into China. There are no special requirements for shipping test articles that are biologics. In the other direction, shipping bioanalytical samples from China to the United States is reliable and customs problems are rare. It takes several days to ship samples from China, through customs, and into a laboratory in the United States.

It is important to be aware, however, that CITES permits are required to ship samples of non-human primates (including plasma, organs, and slides) from China to the United States. (CITES refers to the Convention on International Trade in Endangered Species of Wild Fauna and Flora, an international agreement for protecting threatened species.) CITES permits are an issue for short-term studies of 2 – 4 weeks, because obtaining CITES permits in China takes approximately 13 weeks.

Avoiding delays related to CITES permits is one reason we maintain a bioanalytical lab in China. When client timelines require, Bridge will send a US board-certified veterinary pathologist to China to read slides. For longer studies such as 90-day studies, 13 weeks are well within time limits for dosing animals, and CITES permits are not a problem. Additionally, to avoid study delays resulting from the application for CITES permits, we maintain in-house colony animals and apply for CITES for these animals ahead of time. If we have colony animals available for assignment to your specific study, no CITES permit delay results.

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Bridge handles CITES paperwork for you and will obtain CITES permission covering all non-human primate sample shipments in your study. Fortunately, the 13-week processing period for a CITES permit is a one-time event per study. Multiple shipments within a study do not require multiple CITES permits.

Can we choose to have Bridge do our studies in Beijing or in Gaithersburg?

The choice is yours. We generally have space in both facilities and will work with you to place your study where you decide best.

Are studies placed with Bridge China done completely in China, or are some parts completed in Gaithersburg?

In the future this may change, but for now there are 3 reasons some studies are not completely done in China.

First, currently there is not enough demand to offer developmental and reproduction teratology (DART) in China, so these studies are done only in Gaithersburg. As demand increases, we will reconsider DART as a service offering in Beijing.



Second, we do not currently conduct carcinogenicity studies in China. However, several companies have approached us about carcinogenicity studies there, so this may change as well. We are consulting with biostatisticians and pathologists on building a China facility-based control database for carcinogenicity studies.

Third, as mentioned previously, lack of US board-certified veterinary pathologists based in China sometimes requires slides to be read in the US.

Is there an inexpensive way to evaluate Bridge China’s capabilities before committing to a GLP study?

“We encourage first-time clients to evaluate us with inexpensive short-term non-GLP studies.”

We encourage first-time clients to evaluate us with inexpensive, short-term, non-GLP studies. A pharmacology proof-of-principle study is usually inexpensive. Note, however, that we do not maintain a library of animal models for pharmacology proof-of-principle studies and will need time to set your study up. Also consider evaluating us with a screening protocol for prioritizing compounds for further preclinical development. Preliminary, non-GLP biochemistry and toxicology could be included with a screening protocol. Definitive GLP toxicology studies could come later.

How quickly can Bridge China schedule a 4-week non-human primate study for us?

If colony animals are available, the lead time for a non-human primate study is about 2 weeks. Otherwise, we need approximately 4-6 weeks. We have good suppliers in China who will ship to our Beijing laboratory quickly so acclimatization can begin.



About Ronald J. Marler, DVM, PhD

Dr. Marler is the Chief Scientific Officer and member of the Board of Directors at Bridge Laboratories, a global preclinical contract research organization with laboratories in United States and China.

In addition to his position at Bridge Laboratories, Dr. Marler is an executive administrator at Mayo Clinic Arizona. He is Professor, Experimental Therapeutics and Molecular Pharmacology, Mayo Clinic College of Medicine.

Prior to joining Bridge Laboratories and Mayo Clinic, Dr. Marler was a senior executive with Marion Merrell Dow Pharmaceuticals, Covance Laboratories and Dean of Veterinary Medicine at Kansas State University.

He is Board Certified by the American Board of Veterinary Pathologists and the American Board of Toxicology.



About Bridge Laboratories

Bridge Laboratories is a preclinical contract research organization (CRO) that provides US-level regulatory compliant drug development services globally. Bridge is headquartered in Gaithersburg, Maryland, with lab facilities in the US and Beijing, China. Bridge is known for its extensive work in toxicology. Bridge offers a wide variety of *in vivo* toxicology studies that examine the effect on the immune system, vaccines, developmental and reproductive toxicology, and safety pharmacology. Bridge's AAALAC accredited facility in China was among the first labs to perform GLP studies for clients worldwide.

Visit Bridge Laboratories in Beijing

We'd love to have you and your QA unit visit our Beijing laboratory, meet our staff, and verify for yourself that we have SOPs in place to meet western standards for submission. To arrange a visit, contact us by email or telephone at:

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