smaller companies, the list of compelling reasons for considering China has helped attract significant additional investment in this sector in the past two years. This has had the self reinforcing affect of signaling to potential Western customers that a viable, high quality preclinical CRO sector in China will take root long-term, and that capacity will continue to expand to sustain a substantial cost saving opportunity for an industry struggling with challenging economics due to the soaring costs for developing new drugs. This enthusiasm is moderated to some degree due to uncertainty about how long these cost savings will be sustained, but it is widely expected that total cost savings which are now on average 50%, and will maintain at least at 35% five years from now.

Finally, those companies that consider GLP preclinical safety studies as readily outsourcable and increasingly commodity-like have concluded that the industry will substantially shift outside of the US/EU. Not only is China one of the countries furthest along in offering substantial capacity (due to focused government policies to encourage this sector), the fundamentals support the view that it should be a preferred venue for this industry longer-term. As a result, some companies are now moving to establish priority access and preferred relationships in China to better position them for the long term. For those interested in the ability to support their China R&D centers; this early commitment status offers a degree of input into the services offered by vendors thus providing added benefits to both the vendor and the sponsor.

1.3. Why China: emergence of the China preclinical CRO sector

Beginning over three years ago, many Western companies began to take a great interest in the opportunities for conducting preclinical safety work in China. Several factors appeared to be coalescing to create the potential for China to play an important role in preclinical safety assessment studies; but against a backdrop of great skepticism. Not that long ago, looking off-shore for such capabilities was considered somewhat of a radical notion by many in the mainstream of the preclinical safety assessment community. Virtually all large companies considered preclinical safety testing a core competence, part of the “family jewels” and were disinterested in outsourcing such activities even to local partners. However, the practice of outsourcing preclinical safety testing grew substantially, including GLP studies, to the point that some larger companies now rely exclusively on CROs for this part of their development activities. No longer considered a core competency, the practice of outsourcing took on some of the characteristics of other purchased services, including price competition or pricing sensitivity. While proximity to the customer was still important, many companies
developed the expertise and comfort level needed to working with CROs a plane ride and multiple time zones away.

Against this backdrop, developments in China began to suggest that it could become a venue for a viable Western quality preclinical safety sector and would be relevant to Western pharmaceutical companies in the 2008-2010 timeframe. As part of the Chinese government’s five-year plan, the pharmaceutical industry has been targeted for development. This has led to the availability of significant government funding and incentives to build or modernize many state-owned labs as well as incentives to invest in privately run labs. Private investment in the sector was limited at first, but has subsequently accelerated, with companies such as Bridge Laboratories, WuXi Pharmatech, Frontier Biosciences, and ShangPharma attracting venture, private equity, and public capital market financing. Investors took note of the favorable climate provided by the government and the acceleration of domestic drug development activities which suggested there could be both a robust international and domestic customer base for these services.

From the point of view of prospective customers, the regulatory environment also appeared to be maturing to provide a reasonable regulatory infrastructure for these activities. Concerns about intellectual property (IP) protection and enforcement of IP rights—which have retarded the growth of outsourcing any IP generating activities to China—were easing to the point many believed they were relatively manageable for most preclinical safety testing. At the same time, Western companies took note of the flood of highly trained, experienced former colleagues who were returning to China and available to provide a sound executive and managerial layer for nascent CROs.

Many companies also experienced significant growth in the number of biologics in their drug development pipelines and were concerned about securing reliable access to non-human primates to support their preclinical testing plans. In addition, the sustained double digit growth of China’s GDP put the Chinese market squarely on the map for all major pharmaceutical companies. The increasing potential of the China market to Western pharmaceutical companies meant a growing focus on expanding their development presence in China, and hence investment in China as part of their strategy for establishing a market presence.

The combination and evolution of these factors made 2008 a watershed year for the preclinical safety CRO sector in China. It was a year in which many of the labs in China made substantial progress in three fronts; organizational development, expansion of equipment and
by various levels of government. With the accelerated downsizing of Western pharmaceutical companies in the wake of the financial markets meltdown in the second half of 2008, there has been an appreciable increase in the number of experienced returnees and expats relocating to China. At the same time, some larger Western pharma are continuing to work directly with preclinical safety evaluation facilities, universities, societies, and/or other organizations in China to address training and certification needs within those disciplines in short supply.

As a result of all these developments, the leading domestic Chinese labs (private and public) now possess a level of scientific and technical development as well as the infrastructure, equipment, intent and commitment necessary to offer competitive services to Western clients. Especially in light of the wave of new “Western entrants”, this industry segment has gone beyond the tipping point and is taking hold in China.

1.5. Report Background and Contents

In addition to covering the growth of the China preclinical CRO sector at a macro level, including looking at the infrastructure and environment to support it, this report provides an in-depth look at the capabilities and performance of each of the leading CROs in this segment. The performance of many of the labs has been assessed by the report author and collaborators through structured site visits over the past three years, in many cases multiple times.

Overall, information has been collected on a total of 49 organizations through background research and information sourced directly from these organizations. For over 30 organizations, this information included responses to a detailed 20 page questionnaire. Extensive interviews with Chinese government officials responsible for regulation of, or support for, the domestic pharmaceutical sector were also conducted as part of the analysis of the preclinical safety landscape in China. Since the ability to work at Western quality standards is also dependent on a supporting infrastructure, including providers of such goods and services as feed, bedding, lab supplies, diagnostic kits, and laboratory animals this issue was also explored in-depth.

Facility visits typically took one full day and included a full facility review, a review of lab operations, and discussions with facility and organization management regarding history, current status, and future plans. The facility reviews typically covered receiving, incoming inspection, quarantine areas, general animal rooms, toxicology rooms,
Figure 2.1 below depicts the distribution of labs in China and in the US relative to their degree of compliance with Western GLP practices. As compared to the US, there are proportionately few labs in China operating at a high level of compliance. These labs have been labeled in the chart as the “area of opportunity” since they are today capable selectively of matching the quality level of US and European labs and can thus provide certain China advantages to Western companies under the right circumstances.

**Figure 2.1. Western GLP Compliance Distribution in China and US**

The greatest challenge found at most labs is establishing throughout their organization a sufficient depth of understanding of GLP and animal care principles; the mindset about what is needed and why to become fully GLP-operational labs. Many labs have found that establishing this required depth of understanding at all levels of their organization has taken longer than they had anticipated and have had to adjust their business planning to account for this. As one executive at a chemistry CRO which entered the preclinical safety testing space put it, “If I knew how much more challenging this was, I would have rethought my decision to enter this space.”
Chapter 3

COST COMPARISONS FOR PRECLINICAL SERVICES BETWEEN US AND CHINA

3.1. Comparison Cost Examples

Based on current costs in China, China should present an attractive cost savings opportunity for Western drug developers for the next several years. When comparing the total costs to a sponsor for conducting certain preclinical safety studies in China versus in the US under various scenarios, the typical cost advantage is between 35-50% (see Table 3.1). The maximum per study cost savings one could expect by conducting studies in China instead of the US is approximately 55%. This is based on a comparison of total costs to a sponsor assuming all of the facilities executing the studies are fully compliant with Western regulations, quality standards, and services expectations.

In this table, study description refers to the geography, venue, and strategy for execution. The categories of strategy for study execution are:

Table 3.1. Provides Cost Comparison for Sub-chronic Rat Studies and Chronic Monkey Studies

<table>
<thead>
<tr>
<th>Study Description</th>
<th>Study Type</th>
<th>Study Length</th>
<th>Species</th>
<th>Study Location</th>
<th>2007 Total Cost/Study</th>
<th>2012 Total Cost/Study</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month rat GLP study at China CRO</td>
<td>Sub Chronic GLP</td>
<td>4 weeks</td>
<td>Rat</td>
<td>In China</td>
<td>$ 77,000</td>
<td>$ 99,000</td>
</tr>
<tr>
<td>1 month rat GLP study at China CRO-M</td>
<td>Sub Chronic GLP</td>
<td>4 weeks</td>
<td>Rat</td>
<td>In China</td>
<td>$ 55,000</td>
<td>$ 77,000</td>
</tr>
<tr>
<td>1 month rat GLP study at China pharma</td>
<td>Sub Chronic GLP</td>
<td>4 weeks</td>
<td>Rat</td>
<td>In China</td>
<td>$ 143,000</td>
<td>$ 196,000</td>
</tr>
<tr>
<td>1 month rat GLP study at China pharma, USA pathology</td>
<td>Sub Chronic GLP</td>
<td>4 weeks</td>
<td>Rat</td>
<td>China - US</td>
<td>$ 155,000</td>
<td>$ 207,000</td>
</tr>
</tbody>
</table>

Continued
Histopathology

Some portion of the pathology work—at a minimum peer review, but perhaps much of the histopathology—will need to be conducted in-house by the Western sponsor or sourced through some other Western third party. This will by no means eliminate the cost savings from conducting studies in China but does add to the up front planning and management needed to successfully execute studies.

Study Management and Oversight

Work done in China will, in the short- to mid-term, require greater oversight on the part of the sponsor than work done by CROs in the West. It is well documented that any new CRO relationship, regardless of where the CRO is located vis-à-vis the sponsor, requires a substantial amount of management and oversight during the initial phases of projects. Over time, the client and vendor develop an understanding of each others’ processes, expectations, and practice, and efficient personal relationships are built up. Thus, the time and effort devoted to management and oversight diminishes over the life of the project.

A number of factors drive up management and oversight time and effort initially. First, there are cultural and communication issues that are added to all of the other “relationship startup” issues mentioned above. At several labs, in fact, the English language skills of the lab are such that translators, bi-lingual or third party monitoring staff may be needed to provide this oversight function. Additionally, coordination and logistical complications will add to the overhead of conducting studies in China. For example, for some studies feed may need to be imported for studies. Importing of rodents may also be required in certain instances. Finally, depending on the paradigm employed for oversight, travel costs to China to set up and oversee the studies may add significantly to the total study cost.

Third Party Option

Third party organizations now exist to help select labs, provide up front due diligence, place studies, provide independent oversight on the behalf of the sponsor, and resolve any logistical issues and issues with the CRO’s study conduct. Such services can help reduce greatly the study management and oversight cost and complexity. Companies expecting to place a large number of studies in China will likely over time utilize their own staff—in most cases eventually based in China—to perform these functions. The rate at which these sponsors expand their business with a particular CRO will dictate how long it takes for
the study management and oversight time and effort to approximate that experienced in studies placed with local CROs. CROs that work to ramp up capacity to mitigate this difference factor will likely be more dependent on how fast China is able to address expected shortages of skilled workers such as toxicologists, pathologists, study directors, lab animal veterinarians, etc. than the rate at which it can add bricks and mortar.

**Laboratory Ownership**

State owned, both whole and partial, government labs are prevalent in the preclinical CRO sector in China. State and government ownership can be a somewhat confusing area. With some “government-owned” labs, the situation is quite straightforward. These labs are part of the Chinese government (for example a government ministry or the military) and should be thought of as akin to an NIH or DOD lab in the US. Some may do commercial work, such as the Shanghai Institute of Materia Medica (part of the Ministry of Health—MOH and which has worked closely with AstraZeneca among others) or the National Beijing Center for Safety Evaluation of Drugs (part of the Academy of Military Medical Science).

In the case of the government labs, the ownership, governance picture, and long-term future is quite clear. These labs are not likely to be highly competitive CROs, but they may offer opportunities related to research collaborations, one-off projects, and special capabilities. Government policies, priorities, continued funding, and a host of other issues which are not easily predicted or transparent will limit the degree to which drug developers will utilize them as a major preferred provider for a full range of preclinical safety testing services. Other labs have more complex ownership structures, with the full effect of government ownership and/or involvement difficult to fully assess.

Many of the SFDA labs are in the category of those with more complicated ownership and control pictures. Some are still fully owned by the Chinese SFDA and prioritize government work and a research agenda, while others in this group prioritize their commercial contract research work. Many are already on the path to extensive or complete privatization. In fact, as with many other industries in China, the government has an explicit policy to privatize formerly state-owned enterprises. In these labs, the percentage ownership by the central government has been reduced over time, though some of the new partial owners may themselves be other larger companies that have a significant state ownership as is the case with the Shenyang lab.