

China Pharma Outsourcing: An Overview¹

By Jim J. Zhang, Ph.D.²
JZMed, Inc. (www.jzmedi.com)

Abstract: Chinese pharmaceutical outsourcing industry is playing an increasingly important role in today's world pharmaceutical industry. However, the service capability of this Chinese industry is still limited at present. This situation is due to change soon as consolidations between domestic companies and entrance of multinational service providers are just taking place.

Although a late starter, Chinese pharmaceutical outsourcing industry is catching up extremely fast and presently experiencing an explosive growth. China has become one of the primary destinations for Western pharma and biotech companies looking to outsource. In addition to the constant emergence of new service providers, an increasing number of traditional Chinese pharma companies and R&D-oriented biotech companies are approached by Western companies for partnering. Also, an increasing number of multinational service providers have entered this Chinese market and are bringing in the Western service standard.

Despite fast development, the majority of Chinese service providers are still limited in their service capability. At present there is not a single service provider that is able to provide a fully integrated service covering all areas of drug discovery, development and manufacturing. The whole industry is still segmented. A number of hurdles still stand in front of all Chinese service providers before they could truly become world-class players.

In the past, numerous articles had reported on various occasions a variety of outsourcing activities in China. All information about this Chinese industry was, however, either sporadic or fragmented. Based on the results of a broad survey conducted recently by JZMed, Inc. about the China pharma outsourcing industry, this article provided a complete and up-to-date picture of this Chinese industry including the service capabilities and distributions of Chinese service providers in each technical area of the entire value chain of drug discovery, development and manufacturing as well as the geographic distributions of these service companies in China.

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² Jim J. Zhang, Ph.D. is president and managing director of JZMed, Inc., a market research and outsourcing service company specializing in pharma outsourcing in China. This article was written partially based on the firm's latest research report "Evaluation of Current Service Capabilities of Chinese Pharmaceutical Outsourcing Service Industry". Jim can be reached at 518-477-4831 or jz@jzmedi.com.

Classification of Chinese outsourcing service providers

At present three large groups of service providers make up the entire China pharma outsourcing industry. Each group plays different roles in the outsourcing value chain.

The first group includes those major, traditional Chinese pharmaceutical companies. Historically, the traditional Chinese pharma companies were only engaged in manufacturing and marketing of APIs and off-patented pharmaceuticals for the domestic market. However, largely due to the attraction of low cost coupled with the demonstration of improvement in technology, today, an increasing number of these traditional Chinese pharma companies are approached by Western companies for manufacturing of APIs or pharma intermediates. Among these service providers include those major Chinese pharma companies that were originally owned by the state and presently possess the capability of large scale manufacturing of APIs or formulated drugs under the certified cGMP conditions. Examples include Shanghai Pharmaceutical Group and Harbin Pharmaceutical Group. Both were selected by Pfizer to manufacture APIs for a number of drugs in the steroid series Pfizer has been marketing worldwide. Today, more and more such Chinese pharma companies are selected for partnering. As another example, Shijiazhuang Pharmaceutical Group, another large pharma company in China, recently formed a joint venture with Unigene to build a new facility in Shijiazhuang Economic and Technology Development Zone. In addition, many Chinese API manufacturers have also become such partnering targets. Typical examples include the latest acquisitions of Hisyn Pharmaceutical Co., Ltd. (by Hovione) and Chiral Medicine Chemicals, Co. Ltd. (by Actavis).

The second group of outsourcing service providers or potential targets for partnering are those R&D-oriented biotech companies. Chinese biotech industry is growing rapidly under a favorable environment. An increasing number of R&D-oriented biotech companies emerged in recent years. Many of them have also been recognized by the Western pharma/biotech companies for their capabilities in drug R&D and/or manufacturing of biologics, and thus become interesting targets for partnering. A typical example is the R&D partnership formed between Hutchison MediPharma and Eli Lilly. Another example is Shanghai Sunway Biotech. Co. which was recently approached by Genzyme for manufacturing of Genzyme's gene therapy drug Ad2/HIF-1 α .

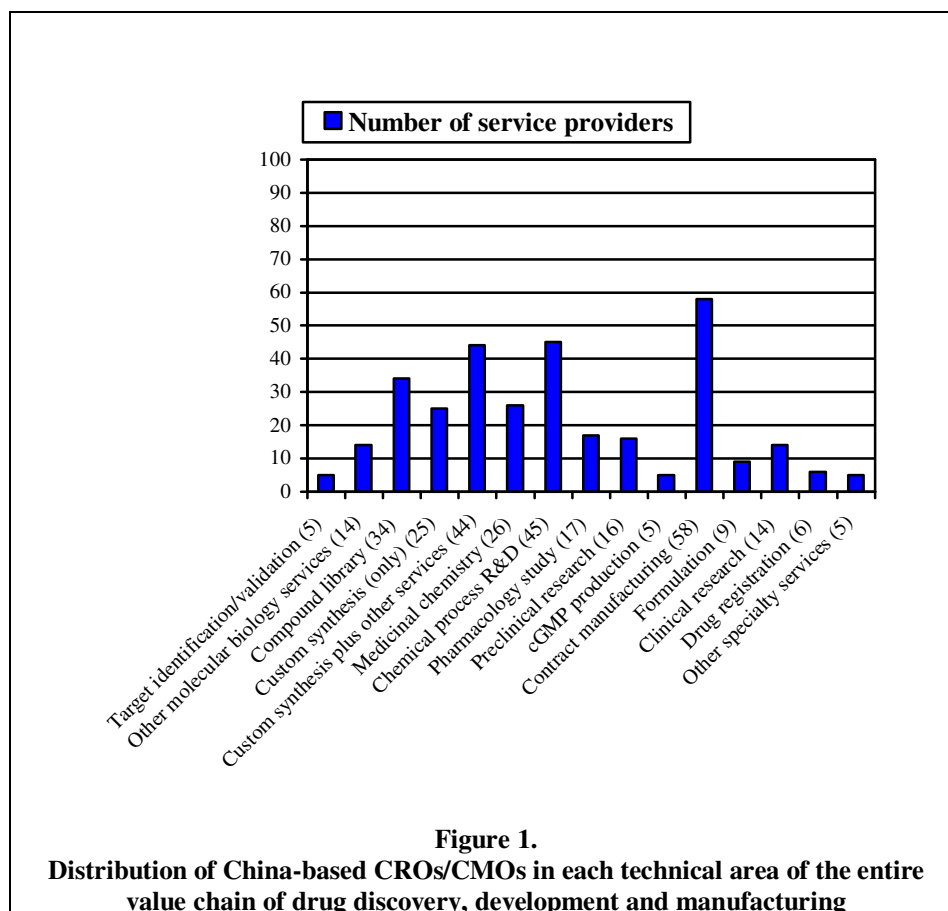
The third group of outsourcing service providers includes those newly emerging, professional outsourcing service companies. This segment is growing much faster than the other two mentioned above. For example, there was no any contract pharmaceutical research service available until 2001. Today more than 250 of such a type of companies provide a variety of services to the pharma and biotech companies around the world. About half of them were founded by the returnees who received advanced education and training in the West. While more new service providers still keep emerging, those early established ones have grown exponentially, both in company size and service capability. For example, five years ago WuXi PharmaTech employed fewer than 300 scientists, but today it owns a scientific staff of more than 3,000. Similarly, ChemPartner, another Shanghai-based CRO but three years younger than WuXi PharmaTech, owns a staff team

of more than 1,300. Both companies recently added preclinical research services to their original chemistry-focused service.

Besides, an increasing number of Western entrepreneur-founded service providers have also been emerging. For example, Bio Duro and Chemizon, both based in Beijing, are founded by American entrepreneurs.

Service capabilities

Coexisting of a large number of outsourcing service providers with various service capabilities provides a great choice to all pharma/biotech companies. Although at present none of these service providers possess an integrated service capability that could cover the entire process of drug discovery, development and manufacturing, combined together, the entire China pharma outsourcing service industry as a whole could provide a full scope of services from target identification and validation to lead discovery and optimization, and further to advanced clinical development as well as manufacturing on large scale of APIs either for commercialization or for support of drug development. Figure 1 shows the distribution of the service providers in each technical area of the drug R&D and manufacturing process.



1. Early stage drug discovery

China currently is one of the hot spots in the world for pharma/biotech companies looking for large compound libraries that possess the structural features of drug-like molecules. China has a huge pool of skilled synthetic organic chemists. Companies specializing in synthesis of specialty chemicals, scaffolds and building blocks as well as isolation and purification of natural products from the Traditional Chinese Medicines (TCMs) spread all over the country. Many rare chemicals that could not be sourced in any other places of the world could be available in China. Also, because of low labor cost and less strictly controlled environment protection, many chemicals that are not profitable to make in other places could be available in China at reasonable prices. This service feature has been extensively explored in the past by many major pharma/biotech companies. Currently, more than 30 such service providers possess focused compound libraries of various sizes.

Chinese service providers are not just able to provide the focused compound libraries. Their service capabilities also cover all areas of the early stage drug discovery. For example, there are more than 15 companies that provide services related to target identification and validation such as DNA sequencing, elucidation of protein structures, reconstruction of proteins, and disease modeling. In addition, there are more than 25 CROs providing services in medicinal chemistry-related research such as lead discovery and optimization, assay and assay method development, pharmacological property study such as determination and optimization of PK and PD. Many of them also possess the advanced techniques and experience such as high throughput screening, computer-aided drug discovery (CADD), and structure-activity-relationship (SAR) study.

2. ADME/Tox study and preclinical research

Currently, there are a large group (about 33) of China-based companies that provide services in preclinical research including *in vivo* efficacy testing, *in vivo/in vitro* ADME screening, plasma protein binding studies, metabolite profiling, and the whole scope of toxicity studies. However, the good quality of service in this sector was not available until recently. The rapid change of landscape in this area is largely attributed to the entrance of a large group of experienced multinational CROs, all lured by the abundant animal species in a favored regulatory environment as well as the readily available manpower resources at low costs. For example, several CROs currently offering services in China are actually the service divisions, branches or subsidiaries of the Western-based CROs. Examples include CrimsonPharma, Bridge Laboratories, and Crown Biosciences. The headquarters of these CROs are all based in the West (mostly in the US) but all or most part of their service is performed in China. In addition, several multinational CROs recently formed joint ventures or partnership with Chinese CROs. Some even acquired their Chinese partner. For example, Charles River Laboratories recently acquired BioExplorer. MPI Research formed a joint venture with Medicilon.

3. Clinical research

Contract clinical research has been conducted in China for more than a decade. In addition to a vast pool of treatment-naïve patients, China also has many specialized hospitals that have concentrated medical facilities, specialists, and knowledge in a special disease area such as cancer. Pharma companies now have also realized that China also has a vast pool of well-trained hospital physicians, thanks to the enormous training provided by many Western companies including multinational CROs and major pharma companies. For example, Astra-Zeneca recently established a training center at No. 3 Hospital of Beijing University to train physicians there for clinical trials. Majority of these medical personnel and other medical resources are localized in major Chinese cities.

So far, most of clinical trials conducted in China were performed by major pharma companies or multinational CROs. Almost all multinational CROs including Quintiles, MDS, PPD, Covance, etc. have their clinical trial centers in China. Many major pharma companies including Astra-Zeneca, Pfizer, GSK, Sanofi-Aventis, etc. also have clinical research centers in China. An increasing number of Chinese-founded contract clinical research organizations also emerged in recent years. At present there are a total of 14 such a type of CROs in China offering services in this sector.

4. Contract manufacturing

Among all service sectors in the China pharma outsourcing industry, contract manufacturing is the most active by far. Service capability of this sector has been greatly improved in recent years as evidenced by the shift of service focus from the manufacturing of pharma intermediates to the manufacturing of APIs. However, many Chinese pharma companies are not professional contract manufacturing service providers. Their service is only on a seasonal basis when a spare production capacity within their organization is available.

At present there are about 70 professional contract manufacturing service providers in China. Majority of them also have strong capability in chemical processes research and development with a decent size of process R&D team as well as advanced pilot plants for step-by-step process scaling up. Their facilities are also generally supported by an internal QC/QA laboratory equipped with advanced analytical instruments (such as HPLC with both regular and chiral columns, GC, LC-MS, etc.). Majority of them have the production capacities from multi-kilograms to low-end metric tons (with reactor volumes ranging from 50 L to 3,000 L) and are able to handle a variety of chemical transformations. Technologies for some special chemistry tasks such as large scale chiral resolution are also available.

Geographic distributions

China-based service providers at present are highly densely localized in two largest cities in China, Shanghai and Beijing, including their vicinity provinces/cities. These two cities contain more than 65% of China's total number of professional outsourcing service providers. Table 1 lists the geographic distributions of the China-based pharma outsourcing service providers.

It is interesting to note that Shanghai is relatively concentrated with more CROs/CMOs in chemistry-related services such as drug discovery research and contract manufacturing, whereas Beijing is more popular to CROs that provide biology-related services such as preclinical and clinical research. This is because Shanghai is a more industrialized city, whereas Beijing is the place where all government agencies are located. Both preclinical and clinical research generally requires regulatory approval. Being physically close to the approving agencies certainly provides an advantage.

Table 1. Geographic distribution of China-based CROs/CMOs in each major city/province

Location (City/Province)	Number of Service Providers
Shanghai	38
Beijing	27
Zhejiang Province	12
Jiangsu Province	10
Liaoning Province	5
Tianjin (including Hebei Province)	3
Chongqing (including Sichuan Province)	2
Guangdong Province	2
Other places	2
Total	101

Major limitations at present

Largely due to the short service history, at present the services capability of this Chinese industry is quite segmented. No single company is able to provide a full scope of services covering all technical areas of drug R&D and manufacturing. One-stop shopping is not commonly available for the time being to many outsourcing companies. More than often, outsourcing companies have to fragment their big projects and separately outsource them to several vendors. On the other hand, special techniques in many providers have still not been established yet.

Most noticeably, even though many China-based service providers are capable enough in developing robust and scalable chemical production processes for any complex compounds, their strong service capabilities in this area are eclipsed largely by the fact that they are lack of additional service capabilities immediately down the stream, that is, the manufacturing of APIs under the FDA- or EMEA-certified cGMP conditions of drug candidates in various development stages. Many times their service is stopped at the stage right prior to the cGMP manufacturing. Today, many Western pharma/biotech companies, in particular, those small- to medium-sized ones, strongly prefer an integrated service from a CRO or a CMO. In other words, they expect the CRO/CMO is able to not

only develop a robust production process but also to further manufacture the API on large scale within the same organization to support their drug candidates in preclinical and/or clinical development. To these companies, it does not make a lot sense if the chemical manufacturing process of a drug candidate is developed by one CRO/CMO, but the actual cGMP manufacturing of this drug compound is conducted by a different service provider, simply because this will waste both time and money as a significant amount of technology transfer is required.

Compared with this situation presently hanging over the entire Chinese pharma outsourcing service industry, almost all Western-based CROs/CMOs in the same service category possess the capabilities in both chemical process development and large scale manufacturing of APIs in their own, certified cGMP facilities. The dearth in familiarity and knowledge of many Chinese service providers about the cGMP regulations limits the overall capability of these companies, and has thus become a weak point at present for the entire industry. Hopefully, this situation will change soon after the FDA opens its China offices.

Future development

Today, the Chinese pharma outsourcing service industry has become one of the major forces in the world pharmaceutical industry. Although at present not many China-based service providers are capable enough to make acquisitions or mergers abroad, having a business operation office closer to customers will be a model for many Chinese service providers to consider.

As more service experience is accumulated over time, it can be anticipated that the service capabilities of many China-based service providers will be enhanced greatly in the next few years. In addition to the vertical growth, more consolidations will also occur in near future, which will certainly integrate the services currently fragmented. It will not be surprised to see in the near future that more Chinese service companies that presently only offer the services in chemistry-related areas will also offer services in biology- and molecular biology-related areas. These service providers will be more favored by small-sized pharma/biotech companies who prefer a one-step shopping task. On the other hand, those small-sized but also well established China-based CROs/CMOs will further strengthen their service capabilities by developing new technologies in various service areas. They will become specialists and thus favored partners for large pharma or biotech companies.

Given the fact that these well-established, China-based CROs/CMOs will coexist in a close geographic location, coupled with their enhanced service capabilities, in very near future Western pharma/biotech companies will find it very convenient to choose a desired service provider from a large vendor pool readily available to any of their specific outsourcing tasks.