

Clinical Trials In China

Is China fulfilling its clinical trial promise?

By **Dr. Faiz Kermani** and **Eric Langer**
BioPlan Associates

CLINICAL TRIALS REPRESENT AN IMPORTANT part of the drug development process and are accounting for an ever-growing proportion of total R&D expenditure. In addition, companies must expand their clinical trial programs in order to meet the demands of regulators and the expectations of patients regarding new medicines. From a commercial perspective, clinical trial data support the product well beyond the approval stage. During the product lifecycle, a drug must be able to compete with a range of competitors and the quality of the clinical trial data will dictate how successful it will be in the long term when rated against them.

As the pharmaceutical market has extended to become truly global, so has R&D. This has become particularly important for clinical trials, as companies believe that their international trials will help them gain rapid access to more patients and also allow them to control costs. Carrying out clinical trials in different markets necessitates working with local physicians, and so an added commercial benefit is that the medical community in these countries will be experienced with the company's products when they reach the national market. In fact, in some countries, regulators expect to see some local clinical development of a product to have taken place.

A growing trend is to use so-called emerging markets, where clinical trial costs are frequently lower than the U.S., Europe and Japan, due to fast patient recruitment and lower operating costs. A decade ago, most companies tended to concentrate their clinical trial efforts in the major world markets, as

data generated here was considered superior to that produced elsewhere. However, the quality of data produced by many emerging market clinical trial centers has improved to the extent that it can be used to support companies when dealing with regulators in large, established pharmaceutical markets, as well as for local efforts. In 2005, AT Kearney estimated that almost half of the 1,200 clinical trials conducted by the 12 largest U.S. pharmaceutical companies included these types of locations¹.

China for Clinical Trials

One emerging market that has experienced a surge of interest with respect to clinical trials is China. The country has a well-established tradition of developing medicines from basic research and the demand for modern pharmaceuticals is growing. Foreign companies are now realizing that these factors are of direct benefit for the conduct of clinical trials in the country. China's popularity has risen to such an extent that it was recently ranked above India and Russia as the most attractive low-cost global location to run clinical trials outside the U.S.¹ To some observers, this finding was a surprise, since the country had an image of being overly bureaucratic and unconcerned about intellectual property rights and regulations.

Dr. Enrico T. Polastro is a vice president and senior industry specialist of the European Pharmaceutical and Fine Chemicals practice of Arthur D. Little. He is based in Brussels. This article was adapted

Yet other developments indicate that China is welcoming foreign investment in clinical research and that it is adapting accordingly. In April 2005, The U.S.-China Joint Commission on Commerce and Trade (JCCT) Medical Devices and Pharmaceuticals Subgroup held a meeting in Washington, D.C. to discuss the evolution of the Chinese market². The meeting featured important industry representation in the form of the Pharmaceutical Research and Manufacturers of America (PhRMA) and the Biotechnology Industry Association (BIO) and was an opportunity for them to put their views directly to the Chinese State Food and Drug Administration (SFDA). In response to questions regarding impartiality towards foreign drugs, SFDA outlined that both imported and domestic drugs were subject to the same regulations and clarified the classification system for drug applications². It also acknowledged shortcomings in the system and the moves underway to align Chinese clinical trial standards with those used internationally. It was generally agreed that this had proved to be a useful forum for constructive dialogue regarding these difficult issues. As a result of this meeting future discussions were scheduled to focus on more specific topics relating to clinical trials in China.

In March 2006, UK Trade and Investment (UKTI), a government department, examined clinical trial trends in China from both from sponsor and outsourcing partner perspectives³. It was clear from discussions with representatives of government departments and local and foreign companies that the clinical trials market was maturing and that there were examples of successful projects that other companies, new to the Chinese market, could learn from. Furthermore, as indicated in a joint publication by the Society for Industrial Microbiology and BioPlan Associates, *Advances in Biopharmaceutical Technology in China*, the high level of investment by foreign organizations shows that perceptions of China being a 'difficult' market have most definitely changed. The publication featured a number of industry contributions on specific clinical trial topics, highlighting the interest of companies in China⁴. The country has become an important pharmaceutical market in its own right and so clinical trial data is invaluable to companies wishing to publicize their products to those seeking modern pharmaceuticals (Figure 1).

Population-related Factors and Clinical Trials

An initial attraction for companies seeking to conduct clinical trials in China is the country's large population (Figure 2). As China represents an estimated fifth of the world's population, it is likely that major diseases found elsewhere in the world will affect a sizeable number of people (Figure 3). However, companies should realize that a closer examination of the make-up of this population will reveal other clues about the potential for running clinical trials and where they should establish centers.

For a start the rate of urbanization has great relevance to the healthcare status of the Chinese population (Figure 4). Although most of the Chinese population still live in rural areas, there has been a rapid rate of urbanization since the 1950s. Urbanization is linked with growth of the industrial

Figure 1: Forecast for per capita drug expenditure in China (US\$)

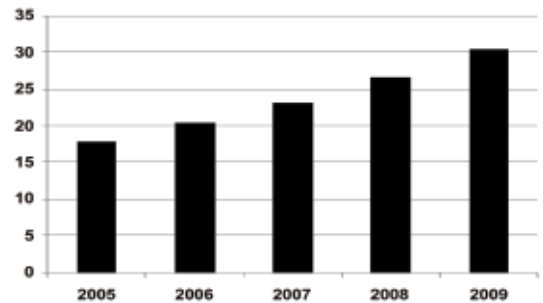


Figure 2: Population Estimates for Selected Asian Countries

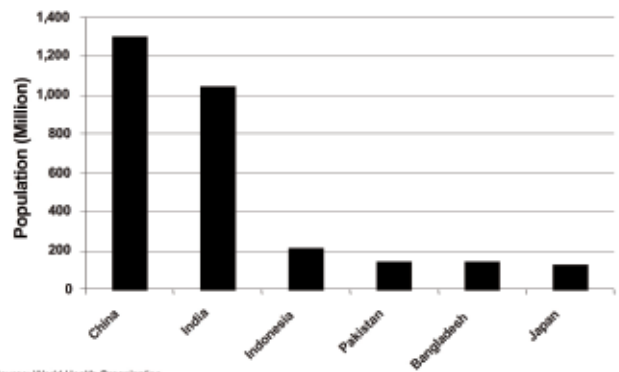
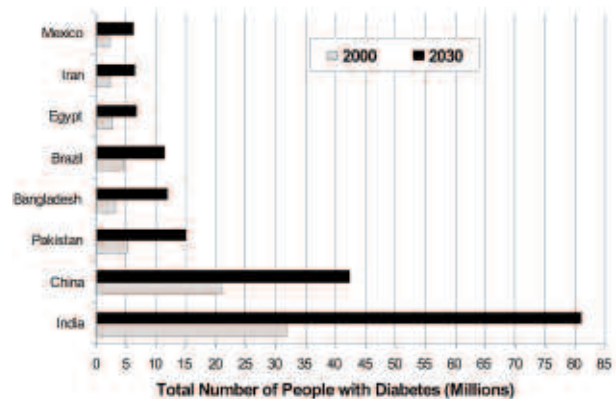


Figure 3: Diabetes estimates and projections in Selected Emerging Countries



economy, but its potential negative effects are rarely highlighted⁴. Rapid urbanization transforms the environment as people compete for limited natural resources and space, leading to overcrowding and poor hygiene.

According to many media reports, China has openly called for greater urbanization. By 2050, it is expected that 600 million Chinese people will shift from rural areas to urban districts⁵. At present China has more than 660 cities and 19,000 towns, but by 2050, 80% of towns will have grown into small or medium-

Figure 4: Urbanization trends in China

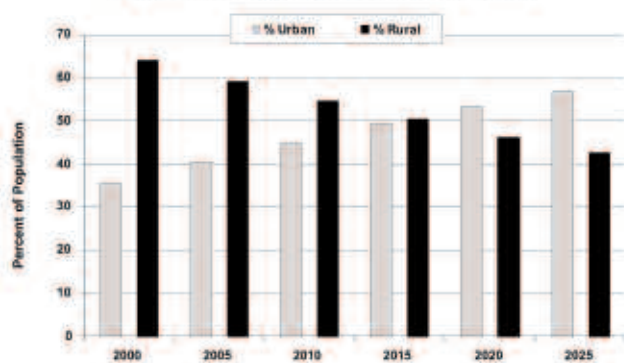
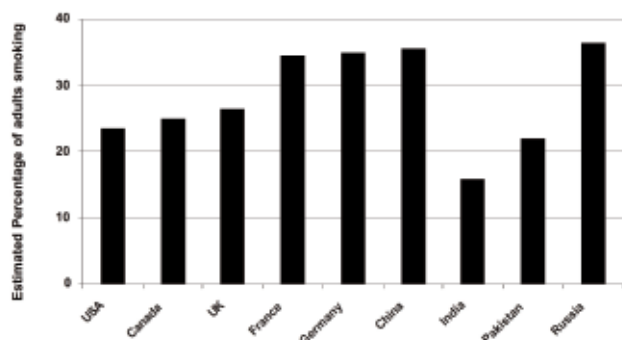


Figure 5: Smoking among adults



sized cities⁵. This will result in the country having 50 ultra-large cities, each with an urban population of more than two million, 150 big cities, 500 medium-sized cities and 1,500 small cities⁵. From an economic perspective, the government and industrialists have welcomed this trend, as they believe that it will boost jobs and stimulate the economy, thereby reducing the wealth gap between rural and urban areas⁴.

The disease profile of urban communities can be very different from those in rural settings. It is likely that the diseases characteristic of urban communities in major industrialized countries will also typify the population of Chinese cities. Generally, the disease profile of urban populations cannot be linked to any single cause, but is due to a combination of various social, biological and environmental factors existent in the urban setting⁶. It has already been noted that the incidence of chronic diseases, cardiovascular diseases, malignant tumors, and mental disorders in urban areas is higher than that in rural areas and it is increasing annually⁶.

Not surprisingly, many clinical trial centers are at hospitals in urban locations as this enhances patient recruitment. For example, many companies have found China to be particularly useful when conducting clinical research in the respiratory therapeutic field. The poor air quality in many Chinese cities has meant that the number of patients seeking medical consultations for respiratory conditions is on the rise and this offers companies a pool of patients who may wish to participate in clinical studies.

Urbanization trends support the view that the respiratory therapeutic area will continue to be one of the major areas for clinical research in China. In its survey of 340 cities by the China State Environmental Protection Administration, none received a Grade I rating for air quality standards measured in sulfur dioxide concentration⁶. Almost 42% of the surveyed cities had Grade II air quality, while 58% scored Grade III or worse⁶. As has been seen in many other major world cities, poor air quality is likely to result in an increase of respiratory disorders amongst the growing population. The likelihood of respiratory illnesses, such as chronic obstructive pulmonary disorder (COPD), is further increased due to the high numbers of people smoking in China (Figure 5). It has been estimated that a quarter of all smoking-related deaths in the world took place in China⁷.

Another important Chinese population factor is aging. In 2000, roughly 10% of China's population was classed as elderly, but the age balance in the population means that by 2050 they will represent 31% of the population⁸. A contributory factor is China's strict one-child policy, which was introduced in 1979. This law was brought in to control the population boom, but it has resulted in a smaller population of younger workers whose contributions can support those who have retired³. There has been a tradition in countries such as China for the elderly to be looked after by the younger members of the family, thus reducing the need for external care services. However, this is changing in modern society and thus there will be more demands placed on the public healthcare system to provide this type of support.

Many foreign pharmaceutical companies have a number of medicines in development for diseases that have a heavy impact on the elderly, such as heart disease, stroke, cancer, and debilitating conditions such as Alzheimer's, Parkinson's disease, diabetes and osteoporosis. Interestingly, there is a widely held view that the elderly tend to be under-represented in clinical trials and so treatments for these age groups are not being developed in the ideal way^{9,10}. It is possible that if pharmaceutical companies engage with the local medical community and patients, China's aging population could be useful in helping rectify this problem. However, it is not only diseases characteristic of aging populations that should be examined but also how clinical treatment should be approached for elderly patients. In particular, there is a need for better management of older patients suffering from cancer. Some authors have pointed out that even the definition of frailty is controversial and that there is no consensus in clinical geriatrics^{11,12}.

These factors illustrate the great potential that China has in terms of clinical trial recruitment. Much of the population is poor, so they have extremely limited access to healthcare and see clinical trials as a means to receive medical treatment and care for free. Pharmaceutical companies should view these positive patient attitudes as a benefit and operate as ethically as possible in order to encourage public participation in drug development. There is considerable media scrutiny of clinical trials in emerging markets, so misconduct by a few disreputable individuals will have a very negative impact for the whole industry.

Costs and Quality

Apart from patient numbers, many companies have been keen to conduct clinical trials in China because of the perceived low costs¹³. In terms of general running costs, it has been estimated that clinical trials can be conducted in China for around 10% of the equivalent cost in a Western country¹³. More specific domestic estimates suggest that Phase I clinical trials in China are 15% of the price in a Western country, while Phase II trials in China cost 20% of the price in a Western country¹³.

These estimates are in line with comments from Sir Tom McKillop, the former chief executive officer of AstraZeneca, who was cited in a 2006 edition of the Wall Street Journal as stating that a major post-marketing clinical trial for two cardiovascular drugs — involving 46,000 patients in 1,250 hospitals in China — cost \$3 million¹⁴. Such a trial would be impossible to run in the West or Japan, to the required standards, for such a low cost.

An additional cost benefit is diagnostic procedure costs. When calculating the costs of a clinical trial, the impact of these types of costs is often underestimated and yet these procedures are essential to the trial from a scientific perspective. Estimates from one Chinese CRO put these types of costs at between 10% and 30% of those for Western clinical trial centers¹⁵. For example, an MRI scan may only cost between \$150 to \$300 and a CT scan between \$100 to \$150.

However, low costs alone can be misleading and clinical trial decision-making must always be linked to quality. ICH GCP is the international ethical and scientific quality standard to ensure that clinical trials involving human participants are designed and carried out in an ethical manner. GCP has its origins in the Declaration of Helsinki and reflects the principles of the treaty: by complying with GCP there is an implied assurance that the rights, safety and general welfare of the trial subjects are protected³. At present there is an ongoing process by SFDA to align Chinese GCP standards with international standards². Foreign companies seeking to operate in China will need to ensure that their Chinese-based clinical trials can meet international standards, otherwise the data will not be of use in supporting product registration when dealing with regulatory agencies such as the FDA and EMEA. With regard to China, FDA has stated that it is willing to accept foreign clinical data provided that the trials are conducted in an ethical manner, they are applicable to the U.S. population, and that the agency can inspect the trial sites if desired².

A number of companies have successfully used clinical data generated in China to support their global clinical programs. Since 1996, AstraZeneca has undertaken nine international multi-center clinical trials in the respiratory area in China, with the involvement of more than 130 domestic hospitals and institutions. The company recently conducted clinical trials for its asthma product, TurbuHaler, in China and used the data to support the drug application overseas¹⁶.

In 2003, Pfizer opened a clinical trial center in Shanghai and stated that not only would the center be concerned with developing drugs for local approval, but would also form part of the company's global R&D network¹⁷. Novartis has been conducting a chronic hepatitis B Phase III clinical trial, entitled the

GLOBE study, at 112 clinical centers in 20 countries worldwide. It is the first international hepatitis B study to include clinical sites and patients in China, with an estimated 25% of the patients enrolled in the GLOBE study coming from Chinese centers¹⁸.

Regulatory Considerations

When companies are interested in running a clinical trial, they tend to approach SFDA first, after which they may choose one of the accredited hospitals for their study^{3,4}. In China, only medical institutes officially certified as "National Institutes of Pharmaceutical Clinical Trials" by SFDA may carry out pharmaceutical clinical trials. At present, affiliated hospitals of the medical universities, some large public hospitals and some special hospitals with unique features can obtain certification. According to one estimate, there are around 145 clinical trial centers and 165 medical institutions in China that possess licenses to conduct clinical trials³. At the investigator level, there is a general interest among the Chinese medical community to be involved in clinical trials and several hospitals have dedicated departments to document their involvement. Chinese physicians are very well respected and therefore are important contacts for companies interested in running clinical trials.

Beijing has around 40% of the nation's hospitals and is therefore an important center for clinical research³. Furthermore, patients from all around the country may travel to these hospitals because of their prestige, thereby giving them a larger patient pool. Beijing's profile as a clinical trial hub is enhanced by the fact that it is the administrative center of the country.

Familiarity with SFDA clinical trial guidelines is essential, particularly as around 45 regulatory changes have occurred since 2005. The documentation for an application for clinical trials must include toxicology data and details of manufacturing standards. Generally it takes eight months to a year for SFDA drug approval³, but in reality much depends on the nature of the drug under trial (see Table 1 on next page).

If a drug to be trialled in China is already available on a Western market then SFDA approval is likely to be quicker. If the drug is to be trialled for the first time in China then regulatory attitudes tend to be cautious, although there can be exceptions. One area where SFDA appears to have been less conservative has been for gene therapy treatments. For example, it allowed SiBiono GeneTech Co.,Ltd to trial Gendicine, a Recombinant Human Ad-p53 Injection product, in cancer patients and eventually approved the product for the Chinese market. This represented the world's first commercial gene therapy product and suggests that the Chinese regulatory system does not necessarily frown upon the testing of innovative products.

Before a clinical trial can proceed in China it must be approved by a hospital's ethics committee. Each one has its own timelines and despite the formalities, the process has been described locally as little more than a rubber-stamping exercise. However, if a drug is considered high risk then timelines can be lengthy and complications can occur in the process. For example, ethics committees are cautious concerning new drugs that

Table 1: Drug classification system for clinical trials

Classification	Description	Implications
Class I	New drugs that are not yet available in the Chinese market or abroad.	Consultation with SFDA on clinical trial requirements advisable.
Class II	Drugs that are available in U.S./EU and are imported to China and need to be checked prior to registration.	Chinese legal requirements dictate that limited samples trial data be submitted. Trials similar to those for local drugs need to be conducted.
Class III	Already marketed in China.	If the sponsor can provide complete dossier then SFDA may waive requirement for clinical trial.

are not yet available in the Chinese market and are being tested for the first time in the country. Similarly, for biotech products for indications such as AIDS, local government approval is also required before a trial may be allowed to proceed.

It should be noted that the ethics committee setup in China tends to not follow the pattern of those in Western countries. At present, many of those who serve on ethics committees at Chinese hospitals are medical doctors from the same hospital. As they work for the very institution conducting the research they are reviewing, there is a potential conflict of interest. Furthermore, they may feel influenced in their decision-making by those senior to them in the institution. International standards require ethics committees to be independent, transparent, and competent in their assessments and decision-making. There remain differences of opinion at the SFDA as to how ethics committees should operate and the types of representatives who should be involved in their activities. SFDA is reportedly considering reforming the make up of these committees to ensure their independence. This could also involve expanding the membership to include laypeople³.

Outsourcing Sector

The increasing popularity of using China as a location for clinical trials has encouraged the growth of the CRO sector⁴. It has been estimated that there are around 100 CROs now operating in China, working for both domestic and foreign pharmaceutical companies on clinical projects. Some have described the Chinese CRO market as being equivalent to that of the European and U.S. CRO markets during the early 1980s. This comparison suggests that the Chinese sector should experience rapid growth over the next decade. Based on SFDA data, during 2005, pharmaceutical companies obtained approval for more than 4000 clinical trials in China. About 30% of this clinical work is believed to have been outsourced, suggesting that around 1,200 clinical trial projects involved CROs in 2005³. If this level of outsourcing were to be maintained over the next

few years, steady expansion of the CRO market is likely to occur.

A number of major international CROs have either entered the Chinese market by themselves or through joint ventures with Chinese CROs. Several Japanese CROs are also operating in China, working with local institutions for clinical trials. Domestic CROs have the view that they can be more cost effective and have better relationships with SFDA and local hospitals. They have described foreign CROs as growing slowly, with their high costs precluding them from working with Chinese companies. In contrast domestic CROs have both the local experience and lower operating costs to attract work from international and Chinese pharmaceutical clients.

Given the influx of foreign pharmaceutical companies, the potential opportunities gained by CROs working with local

companies have received little publicity. Many local pharmaceutical companies have a low R&D-to-sales ratio of around 5%, which means that they carry out relatively little clinical development for innovative products. However, an increasing number of domestic companies are investing heavily in R&D, with 60% of the funds being allocated to clinical trials. While they may be ignored by foreign organizations, local CROs see such domestic clients as an opportunity for them to gain experience and drive their own growth.

Outlook

There is no doubt that China has improved its environment for clinical trials and this is clear from the growing number of projects being run by pharmaceutical companies in the country and the rise of the CRO sector. As more companies enter the market, the relationships they build with local organizations, physicians and patients will strengthen the conditions for clinical research. As the clinical trial sector grows it will need suitably qualified staff and companies will need to play their part in encouraging people to pursue relevant educational courses in this field.

At an official level there are promising signs for the sector. The willingness of Chinese regulators to align their standards with those used elsewhere in the world indicates that commercial clinical trials are seen as beneficial for the country. If the current trends continue, it is not inconceivable that within a decade, companies will consider clinical trial centers in China among their initial choices within their global clinical programs. ■

References

1. Barnes K. China 'most attractive' offshore clinical trial location. *In-Pharma Technologist*. 4 January 2007. <http://www.in-pharmatechnologist.com/news/ng.asp?n=72702-a-t-kearney-china-offshoring-clinical-trials>
2. Anon (2005). US-China Joint Commission on Commerce and

- Trade Medical Device and Pharmaceutical Subgroup
Pharmaceutical Task Force. International Trade Administration,
U.S. Department of Commerce.
<http://www.ita.doc.gov/td/health/jcctpharma2005.pdf>
3. UKTI (2007). The Chinese Biotechnology, Life Science & Pharmaceutical Industry, January 2007. <http://www.uktradeinvest.gov.uk>
 4. ES Langer (Ed). 'Advances in Biopharmaceutical Technology in China', a Society for Industrial Microbiology and BioPlan Associates co-publication, 2006.
<http://www.bioplanassociates.com>
 5. Anon (2002). Experts: China's Urbanization Rate Tipped to Rise. Embassy of the People's Republic of China. News. 19 July 2002.
<http://www.china-embassy.org/eng/zt/wto/t36952.htm>
 6. Lanfranco E (2004). Red Cross to caution China on urbanization. The Washington Times. 6 May 2004. <http://www.washington-times.com/upi-breaking/20040506-125126-8127r.htm>
 7. Haibo L (2005). World's Largest Smoker Legion. Beijing Review. <http://www.bjreview.com.cn/05-03-e/Snapshot-2005-03-1.htm>
 8. Anon (2000). China's ageing population. BBC News. 1 September 2000. <http://news.bbc.co.uk/1/hi/world/asia-pacific/906114.stm>
 9. ACS (2000). Clinical Trials Lack Elderly Representation. American Cancer Society.
http://www.cancer.org/docroot/NWS/content/NWS_1_1x_Clinical_Trials_Lack_Elderly_Representation.asp
 10. Heiat A et al. (2002). Representation of the elderly, women, and minorities in heart failure clinical trials. Arch Intern Med. 162(15):1682-8.
 11. Repetto L et al (2003). Geriatric oncology: A clinical approach to the older patient with cancer. Eur J Cancer 39:870-880.
 12. Aapro M (2005). The Frail Are Not Always Elderly. J Clinical Oncology. 23(10): 1-2.
 13. Raymond E. China lives up to outsourcing hype. In-Pharma Technologist. 16 January 2007.
<http://www.drugresearcher.com/news/ng.asp?n=73400-ukti-pfizer-china-clinical-trials-outsourcing>
 14. Berton E. More Chinese get free drugs in clinical trials. The Wall Street Journal. 14 February 2006.
http://online.wsj.com/public/article/SB113988758015373215-3claQCU2VMtRObREr8e5Rj8AiP8_20060221.html
 15. Engel M (2006). Drug Development in China: Opportunities and Challenges – A Clinical Trial Perspective. The China Life Sciences Partnering Forum – Beijing. <http://www.excel-china.com>
 16. Anon (2006). AstraZeneca and China Medical Association jointly initiate research fund for chronic respiratory diseases. AstraZeneca China Press Release. 27 March 2006.
<http://en.astrazeneca.com.cn/Article/516112.aspx>
 17. Anon (2003). Shanghai to get new Pfizer clinical trial center. China Daily. 5 November 2003.
http://www.chinadaily.com.cn/en/doc/2003-11/05/content_278834.htm
 18. Novartis. New data show telbivudine superior to lamivudine in treatment of Chinese patients with chronic hepatitis B. Novartis Press Release. 27 March 2006.
<http://dominoext.novartis.com/NC/NCPRe01.nsf/44aff02a639be034c1256b4b007b5f4d/095509fa24122580c125713e0026fb4d?OpenDocument>