



EMERGING MARKETS: NAVIGATING THE PATH TO CONDUCT SUCCESSFUL CLINICAL TRIALS IN CHINA

As industry pressure to conduct successful global clinical trials on time and on budget continue, tapping emerging global markets will be crucial to deliver sustained growth to the pharmaceutical industry.

A rapidly changing demographic landscape in China combined with economic pressure for lowercost and faster patient enrollment for clinical trials will continue to make China an attractive solution for pharmaceutical companies.

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Facing global economic uncertainty and expected industry consolidation, many pharmaceutical companies conducting clinical research in multiple countries will experience pressure to develop drugs more quickly and cost effectively, while adhering to International Conference Harmonization (ICH) guidelines with the ultimate goal of a successful regulatory submission worldwide. Pharmaceutical companies competing in the global marketplace will be forced to find new ways to shorten drug development timelines as they compete for internal resources based on cost and compound projected success. Operating under tightening development budgets, pharmaceutical companies will carefully review their partners of choice for outsourcing decisions in development. The most promising late-stage drug pipelines will be funded based upon development portfolio strength. However, speed and cost innovations with regard to how those drugs are brought to market will be factors that pharmaceutical companies cannot ignore. The management of data quality, local regulatory environments, access to necessary patient populations, and highly trained health-care professionals will continue to present challenges for pharmaceutical sponsors, to manage risk in managing large global projects.

Countries with the ability to support clinical trials in a cost-effective, high-quality manner will continue to attract pharmaceutical companies. Sponsor companies will select development partners who are nimble and adept at dealing with local culture, regulatory environments, and stringent safety standards, as well as companies who understand cost and speed in global clinical trial management as critical success factors.

China remains an emerging market for clinical development.

China is projected to be one of the fastest growing markets for the pharmaceutical industry based on population size and demographics, a softened regulatory climate regarding clinical development, and a growing scientific labor pool supporting clinical trials.

- I. **Dynamic market shifts:** China's growing population creates a positive demographic trend in terms of increased consumer demand for pharmaceuticals based on large absolute numbers of Chinese who are adopting a desire to become more westernized. As that population ages and changes lifestyle, western disease states such as diabetes and cardiovascular issues are becoming more prevalent. In addition, there is a growing preference for drugs that improve patient quality of life vs. the more traditional life saving drugs such as anti-infectives.
- II. **Motivation of patients to enroll in clinical trials:** Personal health insurance in China is less prevalent compared to the western world. As a consequence, China possesses larger pools of motivated citizens to enroll in clinical trials in order to obtain necessary drugs and medical treatment not normally available to many Chinese citizens.

III. **Regulatory environment:** An increasingly receptive Chinese government is willing to push for streamlined regulatory process and clinical trial approvals, opening the door to attract western trade. This desire to become a global player is forcing tighter oversight and regulation with regard to protection of intellectual property, particularly in drug manufacturing.

IV. **Large pool of healthcare professionals:** An increasingly educated workforce in China is creating a scientific community capable of providing support for clinical development projects at a fraction of the cost of services contracted in the US and Europe. However, China needs to improve their training environment for those healthcare professionals to bring the standards of care to the level experienced in western countries.

China has appeal as an emerging market.

Large pharmaceutical companies will continue to build infrastructure in China. Novartis and AstraZeneca join an already existing Roche, providing a new round of investment in China-based R&D. These company facilities are being developed in major metropolitan areas such as Beijing, Shanghai, and Guangzhou.¹

Population dynamics favor rapid growth in pharmaceutical consumption.

Sheer numbers in terms of absolute populations, emergence of the new Chinese middle classes, and an increase in prevalent western and aging disease states make China a growth market for pharmaceuticals. As of 2006, China's pharmaceutical market was estimated at 15 billion and projected to grow by 13% annually. By 2010 China is poised to become the fifth largest pharmaceutical market along with the UK and just behind the US, Japan, France, and Germany.² Unmatched numbers in terms of people and the emerging middle class make China a country with a consumer population base desiring advanced health care and quality of life pharmaceuticals, and motivated to seek treatment and therapies. In addition, a shift in the demographics of the Chinese population as an aging population will continue to create demand for drugs in treating arthritis, depression, diabetes, and cardiovascular diseases.

Rapid patient enrollment in clinical trials cuts cost and speeds time to market.

A combination of government investigator sites in metropolitan areas and inconsistent health insurance coverage allow China the ability to quickly enroll patients into clinical trials. A combination of urban-centered populations and their proximity to government-run China State Food and Drug Administration (SFDA) investigative sites, drug-and treatment-naïve patient populations, and a large percent of patients with limited insurance motivates high participation and qualification for clinical trials, driving faster patient enrollment and fostering good patient retention.

1. "China Strides Toward Global Pharma Role", *Chemical and Engineering News*, March 12, 2007

2. "Establishing Clinical Trials in China", *Pharmaceutical Executive Europe*, February 1, 2008

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China will continue to be an attractive target for a rapidly growing pharmaceutical market. However, this great potential comes with a large serving of risk to foreign drug developers. By and large, China's reputation for conducting clinical trials is tarnished from a regulatory and intellectual property perspective. The taint of scandal in recent industry news shows evidence of China's economic tolerance for corruption and disregard for intellectual property as well as questionable safety standards stemming from counterfeit ingredients within the drug and food trade.

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The Chinese government has shown motivation to monitor and make concessions in their quest to become more modernized to invite global trade, such as a Beijing court finding in favor of Pfizer over the Chinese manufacturer counterfeiting Pfizer's drug, Viagra.³ However, change in this arena is slow. Until recently, patent laws for pharmaceuticals were nonexistent and there are still cases of reverse engineering, copying, and counterfeiting. Companies that employ best practices in choosing partners with extensive experience dealing with local culture and regulatory practices, as well as organizations possessing excellent operational experience, will continue to gain advantage in the race to deliver successful clinical trials in China. In order to avoid lengthy regulatory review of trial protocols, it is crucial to plan the trial protocol submission well ahead of actual development timelines.

The risk of regulatory delays must be managed in order to realize the benefits of clinical development in China.

The greatest risk for clinical development in China has long been the delays in approvals at the outset of trials associated with sFDA and ethics committees. Delay issues have long been stumbling blocks based on the unpredictable timeframe for a new compound to be approved for clinical trials. The approval process for a clinical trial depends on a successful march through China's network of complex local and national regulatory bodies, many of whom require sequential review of the approval dossier. Any one delay along this path through the local approval authorities can yield unpredictable timelines averaging anywhere from six to twelve months. Historically, the time uncertainty associated with an investigational drug approved for clinical trials has not offset the shorter patient recruitment cycle typically enjoyed in China.

As of 2007, the sFDA issued an amended measure on the Administration of Drug Registration. The key outcomes of this amendment provided for collective decision-making on clinical trial approvals vs. a single decision maker. A second outcome is

3. Ibid

the provision allowing the drug administration authority to conduct on-site inspections of clinical trial and manufacturing facilities to ensure authenticity, accuracy, and completeness of applications prior to approving a drug for a clinical trial. The Chinese government is becoming more sensitive to the conduct of clinical research, particularly for global pharmaceutical sponsors.⁴ Their ultimate goal is to provide more efficient regulatory systems and stricter rules for drug approval. Their mission at this point is to shorten the approval process for a clinical trial to 90 days, catering to the industry's need to run large multi-national trials. Even with a heightened willingness of the Chinese government to streamline regulatory approvals, sponsors need development partners who possess innate knowledge of the local regulatory authorities and good working relationships with those entities to keep the approval on track.

Lack of regard for intellectual property remains a concern for global sponsors.

China's lack of regard for intellectual property guidelines has long been an obstacle for large pharmaceutical companies who clearly do not want to put drug compound reputation and revenue at risk based upon counterfeit formulations of their products. In 2002, The Chinese government enacted legislation to improve protection of intellectual property in the form of extending patent coverage for 20 years and instituting new provisions for data protection to safeguard a sponsor's investment.

The Chinese government continues to be proactive in working cooperatively with companies desiring to bring technology to China's health-care sector. China's recent membership in the World Trade Organization (WTO) should result in stricter in-country standards. China will be required to improve intellectual property rights and comply with global regulatory standards as required by the WTO. In addition, China recently amended their measures on the Administration of Drug Registration by the sFDA, facilitating faster registration policies, allowing on-site inspections, monitoring trials and manufacturing to ensure quality and safety standards are met, and encouraging private company recall processes.⁵

Trained health-care professionals are emerging in greater numbers from Chinese universities, allowing clinical trials to be conducted on a lower cost structure basis. However, there are still training issues to be addressed with regard to global GCP guidelines.

In addition to locally trained scientists, there is a great movement for Chinese scientists, many of them educated in the US, to return to China making jobs in clinical development attractive. This new influx of scientists is creating a medical community of greater numbers engaged in rapid modernization of medicine to western standards of care. These professionals, along with the Chinese government, are highly motivated to embrace drug development as one means to participate in the emergence of China as a modern culture. Based on a large labor pool of doctors, scientists, and laboratory technicians, trials can be conducted in China at a fraction of the cost compared to the US due to large local labor pools, lower overhead, and lower cost of living standards.

4. Ibid

5. "The Regulation and Approval of New Drugs in China", Tufts Center for the Study of Drug Development, as reported by *R&D Directions*, January 2009

Better training is needed in GCP and safety standards for Chinese health-care professionals.

While there is an emergence of highly educated health-care professionals, many need better in-depth training on GCP standards. Globally operational CROs in China have a large advantage over local CROs. This is based upon the advantage that global CROs have with regard to thorough training and development to mirror the US and European standards for more regulated quality and consistency in clinical trial development and management. A sign of progress for Chinese research centers: in December of 2008, the Association of Clinical Research Professionals (ACRP) announced they had entered into an alliance with the Shanghai Clinical Research Center (SCRC) to promote ACRP standards of research and develop training centers in multiple locations in China. A combined focus on quality and safety standards comprising best practices in clinical development in terms of GCP and ICH guidelines will continue to evolve throughout China as a result of the agreement.⁶

While the risk of conducting trials in China can be daunting, the ultimate reward offered by China as an emerging market cannot be ignored. Lower overall costs and faster speed through the development process outweighs the risk if a best practices mentality is adopted from the outset by enlisting a strategic partner with in-country capabilities and expertise.

China represents an attractive pharmaceutical market. As major pharmaceutical companies consider expansion to capture these off-shore markets, CROs are well suited to direct and manage the clinical trials for these multi-national projects. In fact, China is a witness to growth in this sector as CRO partnerships allow pharmaceutical companies to alleviate and manage risk in uncharted waters by partnering with CROs who have specific expertise at managing global trials with special knowledge of China.

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For large pharmaceutical companies to successfully conduct clinical trials in China, they must partner with a CRO with an established reputation in China, dedicated resources, and therapeutic expertise. Knowledge and experience with local regulatory bodies make the likelihood of success that much greater.

Why Partner with a global CRO in China?

CROs operating on the ground in China will continue to provide the most attractive options to pharmaceutical companies to manage their clinical development projects. The strategic nature of these local partnerships allow pharmaceutical companies to tap deeply into the CRO's therapeutic expertise and access necessary country patient populations for lower cost and better efficiencies vs. managing the cyclical nature of their development calendars internally.

6. "ACRP Enters Alliance with Shanghai Clinical Research Center", ACRP Press Release, December 2008

Adding a CRO with a local presence in China can generate a real benefit by allowing pharmaceutical companies to access a mix of sites domestically and internationally and leverage efficiencies by running trials simultaneously in multiple countries, while enjoying patient enrollment for faster development using emerging markets. In nascent countries like China, where clinical development is rapidly growing but challenges remain, best practice would dictate choosing development partners with deep expertise in other countries as well as solid experience navigating the local Chinese waters.

Medpace offers wide range of capabilities in China.

- I. Industry experts who have extensive local relationships with the Chinese sFDA and other local regulatory bodies
- II. State of the art facilities, including central laboratory capabilities (Medpace Reference Laboratories, China)
- III. Real world experience in conducting clinical trials in China
- IV. Full-service capabilities locally and globally

I. Strong local regulatory experience in China, including intimate sFDA operational knowledge, IND dossier compilation, IND submissions, and NDA preparation and submissions.

A strong therapeutic team with expertise and hands-on knowledge of drug development requirements in China and in-country medical monitors to oversee projects allows Medpace to conduct operations with confidence and a high success rate. Located in Beijing since 2004, the Medpace local presence has resulted in the formation of strong local project teams. A staff of 18, including a General Manager and Medical Monitor ensure consistency and compliance for local Chinese trials as well as larger multi-national trials.

“We are excited about the opportunity for drug development in China,” according to Dr. Wei. “We have expertise to manage clinical trials for global firms as foreign data to support their global registration, and are able to help foreign firms find their Chinese domestic partners to co-develop their drug product supporting their local regulatory submission to enter the Chinese pharmaceutical market.”

Medpace Medical Director, Xiaoxiong “Jim” Wei, MD PhD, is a notable industry expert with extensive US FDA experience and hands-on relationships with the Chinese sFDA and on-site country managers. These relationships, combined with a dedicated group in the Medpace office in Beijing, provide the necessary knowledge to conduct trials for local Chinese entities as well as global trials for US and European based pharmaceutical sponsors.

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II. State of the art central laboratory facilities (Medpace Reference Laboratories in Beijing) allow Medpace to operate locally or as a key country site within a larger global trial.

The recent addition of the Medpace Reference Laboratories (MRL) in Beijing allows Medpace to integrate all laboratory services with local investigator sites. China allows no export of biologic materials. Therefore, the ability of a development partner to offer local central laboratory services ensures that data integrity and safety standards are standardized in accordance with all participating countries in multi-national trials.

The Beijing facility adds full central laboratory capabilities in a 30,000 sq. ft. facility housing both the laboratory and CRO with full project and data management capabilities. Investment in full-service capabilities and central laboratory services ensures that quality and consistency of data is in line with Medpace global quality standards. The laboratory equipment is fully owned and supported by Medpace, making all services within China identical to global standards of data integrity and consistency.

III. Real world experience

Our current experience in China includes a large global cardiovascular endpoint trial involving 1,500 patients in 38 clinical centers in China.

IV. Full-service capabilities

A full suite of clinical development services are currently offered, including Clinical Trial and Regulatory Submissions, Project Management, Medical Monitoring, Clinical Monitoring, Data Management, and Imaging as needed. A fully staffed group of scientific professionals, including a General Manager, Medical Monitor, Clinical Trial Manager, and other support clinical positions ensure operational integrity.

Medpace utilizes proprietary software, Clintrak[®], a study management system facilitating team coordination and providing decision support for sponsors, sites, and Medpace to ensure the global team is focused and organized for maximum efficiency using a common data platform. Medpace data management has the ability to apply GCP and IHD-match consistency of data in each country at the same quality levels as the US.

All associates are Medpace employed and trained to the same high Medpace standards with regard to SOPs and operational excellence worldwide.

Profile

Dr. Xiaxiong “Jim” Wei



Jim Wei, MD, PhD, has been the Director of Clinical Pharmacology since 2007. Dr. Wei came to Medpace after working as a Senior Reviewer in the FDA Office of Clinical Pharmacology for nearly 10 years. At the FDA, Dr. Wei was directly involved in reviewing INDs and NDAs for the Division of Metabolism and Endocrinology Products (anti-diabetic drugs, lipid-lowering drugs, insulin products, hormonal drug products, anti-osteoporosis, and anti-obesity drugs). Dr. Wei has extensive experience in the clinical trial regulatory aspects of early phase cardio-metabolic studies. He has presented many topics on drug metabolism/drug interaction, pharmacogenetics, and risk assessment in drug development at regional, national, and international conferences. In China, he has addressed such international conferences as the *Impact China IV Conference* in Beijing, the *International Workshop on Mass Spectrometry and New Drug Development* in Hangzhou, and the *International Society for the Study of Xenobiotics* in Shanghai. He has also published more than 20 peer-reviewed articles and book chapters, is certified by the American Board of Clinical Pharmacology, and is a member of the American Society of Clinical Pharmacology and Therapeutics.

Medpace Reference Laboratories, China

Medpace recently opened their new offices in Beijing, China, housing a full-service CRO and the state-of-the-art Medpace Reference Laboratories, China.



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