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WHITEPAPER

# Opportunities and challenges for clinical research in China

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# Abstract

Today China is a dominant presence in the clinical trial arena and one of the most desirable biopharmaceutical markets in the world. This is expected to continue for decades to come. China is the world's most populous country (1.4 billion), with an aging population experiencing a rise in chronic diseases associated with Western lifestyles, and a sharp increase in infectious diseases. Globalization has provided China with an economic boom, and Western pharmaceutical companies can realize significant opportunities to escalate drug development and reduce costs. Barriers do exist, including logistics, language, and cultural aspects. In China's business environments relationships are invaluable.

Thermo Fisher Scientific is well-established in the Asia Pacific region with two facilities in China (Beijing and Suzhou) and an impressive 20-year track record. This whitepaper presents the opportunities—and challenges—of conducting clinical trials in China, together with proven strategies for success.

# Introduction

China's dominance in the clinical trials arena began about two decades ago, with the pharmaceutical industry's embrace of globalization to reduce burgeoning development costs and timelines. Research and development (R&D) investments in Asia-Pacific soared between 2000 and 2010, with China emerging as the leading player.

In addition to being the world's most populous country, China has an aging population, offering biopharmaceutical companies an unrivaled opportunity to recruit study subjects from a dense pool of patients. With economic development has come an accompanying rise in chronic diseases usually associated with Western lifestyles—including heart disease, diabetes and cancer—along with a sharp increase in infectious diseases. Add to this an improved infrastructure, a rich pool of well-trained healthcare professionals and the relatively low cost to conduct trials, and it is obvious why China is a draw for firms researching and marketing new pharmaceutical products.

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Recent regulatory reforms have shortened the timeline to approval and increased investment in the country. In 2018 the National Medical Products Administration (NMPA)—formerly known as China Food and Drug Administration (CFDA)—introduced a new policy that changed the clinical trial authorization (CTA) official review and approval process to a 60-day waiting period, similar to the US FDA's evaluation/approval period.

Additionally, NMPA is also now able to accept clinical data from international clinical trials for new drug registration applications (NDAs). These significant policy changes, coupled with a 6x increase in the number of reviewers at the China Center for Drug Evaluation (CDE) have reduced the application backlog from an average of 4.5 years in 2015 to less than 60 days in 2018.

At the same time, more stringent regulations have introduced processes such as self-assessments and on-site inspections which are now required for NDA approval. GMP standards are being tightened and enforced, bringing China closer to the USA and EU guidelines. These changes have improved quality and, at the same time, significantly reduced the number of applications in the pipeline, enabling a faster review cycle.


In spite of these improvements challenges still exist. Reaching patients in a sprawling geographic region, navigating complex import processes plus language and cultural barriers require local infrastructure, experience and expertise.

Thermo Fisher has been partnering with sponsors to conduct clinical trials in the Asia-Pacific region for two decades. Today, Thermo Fisher operates seven facilities in the region, including two in China, where it is the major clinical importer. This paper examines the opportunities and challenges of conducting clinical trials in China, and offers proven strategies for overcoming hurdles.

## Opportunities for clinical trials

About two decades ago, pharmaceutical companies craving cost savings and faster drug development turned to globalization as a solution. Globalization proved to be a resounding success, both for the industry and for China.

The rapid migration of clinical trials to the Asia-Pacific region enabled companies to lower research expenses, speed patient recruitment and establish footholds in developing markets. China soon emerged as the most desirable global location for conducting clinical research, according to industry surveys. Numbers bear that out. In 2007, 1% of trials registered on US government portal clinicaltrials.gov included a Chinese study center. By late 2019 China-based registered trials that were active and enrolling numbered 5,000+, over 9% of all registered trials.

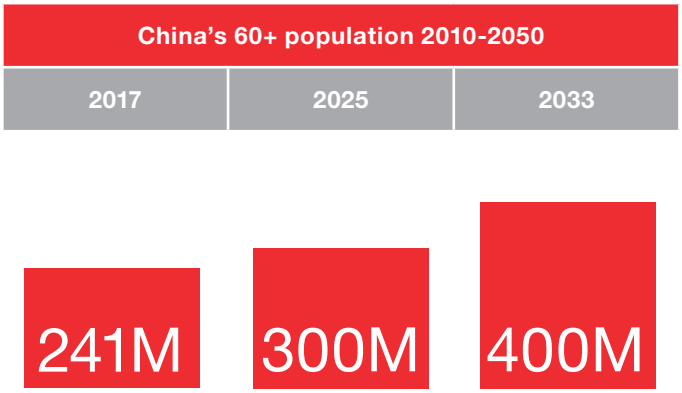
The steady flow of research and other dollars stimulated rapid economic development for the entire Asian market. Forecasts for China are even more optimistic. Ranked as #2 for Gross Domestic Product behind the United States, some analysts predict it could take the top position as early as 2020[1].

By 2021 the Asia Pacific pharmaceutical market, which in 2017 was already the second largest in the world after North America, will have increased its lead over Western Europe in third place and made gains on North America. Advanced countries, such as China, are experiencing consistant double-digit growth rates[2].

At a time when the complexity, duration and cost of clinical trials are on the rise, China has established itself as an ideal clinical research location for a host of reasons.

The reasons range from the size, age and density of the patient pool to the speed and cost of patient recruitment. Among them are:

- **Sheer numbers.** The population of mainland China is about 1.4 billion people, more than any other country in the world.
- **Graying population.** Due to low mortality and the strict one-child family policy that has been in place for decades, China's population is aging and beset with a growing list of age-related health issues. By the end of 2017, the number of Chinese aged 60 or above had reached 241 million, representing more than 17 percent of the country's population. The figure is expected to peak at 487 million, or nearly 35 percent, around 2050. The share of expenditures spent on elderly nursing services and health care on the country's GDP will rise from 7.33 percent to 26.24 between 2015 and 2050[3].




- **Western patterns of illness**. Economic growth, resulting in diet and lifestyle changes, has led to an increase in chronic diseases usually associated with Western countries. Heart disease, chronic respiratory diseases, diabetes and neurological disorders are among the top 10 causes of death. Meanwhile, increasing mobility has led to a specific focus on infectious diseases such as HIV/AIDs, tuberculosis and influenza[4].

- **Dense patient pool.** Thanks to urbanization and industrialization, more than half of all Chinese now live in cities, a proportion that is expected to increase. Where in 1980 the World Bank stated 19.6% of the Chinese population had been living in urban areas, by 2017 the number had grown to 58%. Today, Shanghai, the world's largest city, has a population density of 9,900/sq. mile vs. the country's average of 375/sq. mile.
- **Talent pool of healthcare professionals.** The number of healthcare workers trained in Western medicine—including doctors, physicians' assistants, registered nurses and pharmacists—has grown tremendously in conjunction with ongoing healthcare reform.
- **Improved infrastructure.** The Chinese government is investing heavily to improve the country's infrastructure. These efforts—including new and improved roads, rail and metro, ports and airports, and utilities such as water supply, waste management and energy—are facilitating socioeconomic development in China. Another important element of the country's improved infrastructure is the growing number of hospitals and healthcare facilities, all of which are state-run.

Given these many advantages to conducting clinical trials in China, it is no wonder that this sprawling nation tops every sponsor's clinical site wish list.

## Challenges abound despite advantages

Benefits notwithstanding, there are hurdles to overcome in conducting clinical trials in China.

While patient recruitment is often faster and relatively inexpensive, for example, logistics can be costly and time-consuming. This is a more significant problem for trials of high-value biologics, which must be shipped and stored in the cold chain at controlled temperatures.

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Other obstacles include language and cultural issues and bureaucracy, including evolving government policies and regulations leading to long timelines. Here are the key hurdles to overcome:

- **Transportation issues.** The sheer vastness of China, the world's second largest country by land, presents formidable logistical and transportation challenges. China is divided into 22 provinces, extends across much of East Asia and borders 14 nations, more than any other country except neighboring Russia. China also has more than 180 commercial airports and over 2,000 rivers and seaports. Transporting clinical supplies in a country that boasts the world's longest highway system, the busiest railways in the world and the largest market for cars is no small task, especially considering that traffic jams in cities such as Beijing and Shanghai can reach legendary proportions. Consider the impact these local transportation issues can have on a typical international transportation of clinical supplies, which can easily consist of multiple airports, ground handlers, airlines, truckers, freight forwarders, customs brokers, country regulations and climate zones.

- **Language.** Language continues to be a major issue in China. Although the official spoken language is Mandarin, English is the language of business. English language skills in China are relatively good compared with other parts of Asia, and China boasts the world's largest number of English language students. While the importance of Mandarin is expected to grow along with China's global economic impact, Mandarin is not their only language by any means. China boasts eight primary dialects and 292 living languages. For instance, in Suzhou (pronounced *Soo-Joe'*), residents speak Suzhounese, part of a primary dialect known as Wu.

- **Cultural barriers.** The country's distinct culture poses significant obstacles to outsiders conducting business. In other parts of the world, business is routinely conducted long-distance, thanks to email, conference calls and Skype, often among partners who may never meet face-to-face. In China, however, the emphasis in conducting business is on contacts rather than contracts. Establishing relationships based on mutual respect is a fundamental aspect of both the culture and business environment. Professional relationships are built over time through face-to-face social interaction.

- **Import/export requirements.** Constant updates in import-export requirements add to the already complex environment of conducting clinical trials in China. A complex web of ever-changing national, regional and local government policies—and differing interpretations of what they mean—can trigger jurisdictional disputes over documentation. Such disputes often take considerable time to resolve, delaying shipments of temperature-sensitive materials and the start of trials.

- **Budget control.** For cultural reasons, pricing in China is highly variable. This is especially true with respect to Phase IV and investigator-sponsored studies, whose budgets are held locally in China in local currency. These varying costs for services require careful examination. For example, it may be possible to save on packaging while paying more for logistics.

- **Changing regulatory landscape.** As the number of clinical trials taking place in China has grown, so too have the regulatory policies governing them. The rules regarding clinical trials evolve constantly. In 2014, for example, China added new requirements for hospitals running clinical trials, including internal rules and standards of procedures for administering clinical studies, the centralization of study financing at the hospital level, and a mandate for constant trial supervision.

As China's role in global clinical trials grows, it remains to be seen how these issues will play out and standards will harmonize.

## Making it work: Top recommendations for managing clinical trials in China

With nearly two decades of experience under their belts, Thermo Fisher supply chain managers know what works—and, just as importantly, what does not work—with respect to conducting clinical trials in China.

As a supply chain industry leader, we establish best practices, upholding GMP standards and sharing global expertise with sponsors and regulatory authorities.

At our Beijing and Suzhou facilities, well-established teams of Chinese nationals apply local knowledge and language skills to address the needs of sponsors in ways that are both efficient and culturally acceptable to all. Here, these veteran team members share their recommendations about how to navigate the Chinese clinical trial environment to preserve resources, avoid frustration and assure success.

**Stay up-to-date on clinical trial regulations and observe them scrupulously.** Because clinical trial regulations in China change constantly, it is critical to stay current on requirements and comply with them completely—or face the prospect of delays.

- Work closely with National Medical Products Administration (NMPA) officers and prepare meticulous documentation. It goes without saying that documentation should be complete and accurate, and should include an extremely high level of detail—e.g., required Investigational Medicinal Products (IMP) expiry dates, the unit value of the drug on the pro-forma invoice, and a myriad of other pieces of information.

- Keep in mind that requirements differ by port of entry. Note internal distribution requirements with respect to dangerous goods, and work only with approved brokers for trials involving controlled drugs.

- Be sure partners offer knowledge, experience and contacts, for which there are no substitutes in China.

- Words of warning: Should customs authorities merely suspect any wrongdoing—such as an inaccurate declaration of import value, for example—a lengthy delay and investigation will ensue. Lastly, be aware of the provisions of the Foreign Corrupt Practices Act (FCPA), a subject of heightened awareness in China and prosecution in the U.S.

**Prepare supplies in advance for maximum readiness.** Take full advantage of the time awaiting CTA approval to ready all clinical supplies.

- Do everything possible in advance, such as sourcing comparator; packing, labeling and preparing all kits; and planning distribution models to accommodate patient recruitment predictions. In short, ensure that supplies are ready for an immediate trial start when the NMPA grants the go-ahead.

- Consider manufacturing and packaging in a Free Trade Zone (FTZ), the advantages of which include tax and duty-free status in China for studies conducted outside the country. Sponsors pay tax only on supplies that cross the financial border to China from FTZs and enjoy the added advantage of proximity. For example, from our Suzhou facility, which is located in a FTZ near Shanghai, it takes less than a half day for supplies to reach domestic cities such as Beijing. Staff at both the Suzhou and Beijing facilities are well versed in import/export and regulatory requirements, mitigating risk across the supply chain by minimizing the number of hand-offs required during the transport of clinical supplies. More than 90% of supplies reach sites within 24 hours, with shipments scheduled in consultation with investigator sites to accommodate storage/inventory control requirements and patient schedules.

**Ensure the smooth importation of supplies.** Globally, customs delays are the most common reason for extended delivery time of supplies. Customs delays can lead to temperature excursions, especially if inspections take place, so avoiding them is critical.

- One key to ensuring a hassle-free experience in China is choosing the right Importer of Record (IoR). The Importer of Record is a legal entity responsible for ensuring that imported goods comply with local laws and regulations, filing completed duty entry and associated documents, and paying assessed import duties and other taxes on these goods.

- Understand the import process and timelines and, as discussed above, ensure that documents are in order and contain all necessary details before shipping. Always have valuation evidence on hand to defend the level for duty or tax payments.

- Seek out service providers with a focus on chain of custody and a low rate of inspections, the benefit of having established long relationships of trust with the importer and customs officials.

- Minimize handoffs within the supply chain and ensure that all parties appreciate the temperature sensitivity of cold-chain supplies. As a leader in cold-chain shipping, Thermo Fisher has proven capabilities in the storage, handling and distribution of temperature-controlled supplies. The company monitors all shipments and implements processes to prevent temperature excursions. Furthermore, our excellent relationships with couriers and Chinese customs officials mean smooth transportation through customs and a minimum of inspections.
- Finally, schedule shipments for the work week, not weekends, and always have an experienced local presence on hand who understands local customs and can help resolve issues in the local time and language. In China, always choose experience over promises.

**Engage the right expertise to maintain high standards and deliver reliable outcomes.** The NMPA has recently recognized the need for clinical packaging operations to meet Good Manufacturing Practices, proving that setting and upholding high standards across the entire supply chain is essential. GMP is a requirement in the international marketplace and the default standard for all global sponsors.

- Partner only with organizations that have established track records of working to similar global standards. Meanwhile, contract with approved organizations to monitor and audit all parties involved in the supply chain to ensure that standards are maintained.
- Make sure providers have clear GMP compliance and can provide an external audit certificate from an independent inspection, verification, testing and certification firm, such as SGS.
- Look for adherence to Good Distribution Practices (GDP), a subset of GMP, as well. As standards harmonize, this will be increasingly important.
- Ensure that anti-corruption policies, the subject of vigorous investigation and prosecution in China, are upheld. Should risks be identified, enhance due diligence.
- Maintain control and use only experienced providers with multilingual capabilities to help clients manage any challenges that may arise, such as customs inspections, valuations and paperwork.

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**Apply best practices in late-stage customization and management of supplies.** Emphasize expertise and flexibility to increase productivity. Effective supply management can make it possible to:

- Commit inventory late in the process without negatively impacting the trial pool supplies
- Perform local packaging and late-stage labeling in a GMP environment
- Allow fast turnaround, with the ability to create and approve batch records locally
- Adapt supplies to accommodate site recruitment
- Minimize wastage by using inventory and cash flow efficiently

While it is possible to accomplish all of this in China today, doing so requires a partner with experience and capabilities. Look for the following: A robust Information Technology (IT) system specifically designed for clinical trials; relabeling capabilities, including that of performing complex labeling using variable text; and resources necessary for repacking kits – all within a GMP environment.

**Take a holistic approach by viewing the supply chain from end-to-end, i.e. from sponsor to investigator site.**

**Manage the entire supply chain, from start to finish.** Take a holistic approach by viewing the supply chain from end-to-end, i.e., from sponsor to investigator site. This includes considering costs across the entire supply chain, including study design, manufacturing, packaging, distribution, returns and destruction. Always be in control and in compliance, while maintaining visibility:

- Use tools and technology to ensure a complete chain of custody, with support to intervene and resolve issues on your behalf should anything go awry
- Engage data-driven courier analysis to define the best distribution model
- Establish a relationship of trust with customs officials
- Meet requirements to facilitate smooth importation of supplies
- Minimize hand-offs to mitigate risk
- Plan shipments to meet site expectations and needs
- Clearly define roles and responsibilities for all parties
- Predict timelines as best as possible, but allow for delays

**Embrace contingency planning.** Contingency plans should include the timely resupply of clinical materials. Be sure to adjust the parameters in the Interactive Web Response System (IWRS) to ensure that they match revised trial schedules.

**Remember, we are working to improve patients lives.** Consider the needs of the patient above all else. For example, deliver the right quantity of supplies to the right person and place at the right time and in the right condition. Patients in China often travel a long way to participate in a clinical trial and may not have easy access to transportation, so returning if study supplies are not available can be difficult. Also, make study participation easier for patients by not giving them large or heavy packages of supplies to carry home.

**Maintain a local presence.** There is no substitute for local knowledge, experience and contacts in China. Maintain a local presence or work through a trusted and experienced local intermediary for smoother business relationships and transactions. Having a local presence on hand to resolve issues as they arise—operating in the local time and language, armed with connections and an understanding of customs—is absolutely invaluable in China.

**Above all remain flexible. "If one has a flexible attitude, one knows how to deal with changing situations." A Chinese Proverb Quoted in Du Wen Lan, 1815-1881, GuYaoYan**

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## About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 65 locations around the world, we provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vectors, cGMP plasmids, formulation, clinical trials solutions, logistics services and commercial manufacturing and packaging. We give pharma and biotech companies of all sizes instant access to a global network of facilities and technical experts across the Americas, Europe, Asia and Australia. Our global leadership is built on a reputation for scientific and technical excellence. We offer integrated drug development and clinical services tailored to fit your drug development journey through our Quick to Care™ program. As a leading pharma services provider, we deliver unrivaled quality, reliability and compliance. Together with our customers, we're rapidly turning pharmaceutical possibilities into realities.


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