

Best Practices for Managing a Global Clinical Supply Chain: A Spotlight on China and India

At a time when bringing a drug from laboratory to licensure takes \$900 million and up to 16 years, pharmaceutical companies seeking solutions - including cost-savings and rapid patient recruitment - have made China and India the top-ranked locations in the world for off-shore clinical trials.^{1,2}

The increase in the number of clinical trials migrating to cities like Shanghai and Mumbai has been accompanied by a host of challenges from a clinical supply chain perspective – challenges that range from addressing local inexperience in conducting trials and navigating a web of evolving government regulations for drug importation, to ensuring Good Clinical Practice (GCP) at trial sites, and managing complicated logistical issues in sprawling countries plagued by limited infrastructure.^{3,4,6,9}

As the number of clinical trials has increased they have also become more complex, thanks in large part to double-digit growth in the number of studies for biologic products that require controlled temperature conditions during shipping and storage. More than a third of Fisher Clinical Services' projects, for example, now involve controlled temperature products that require significant supply chain management and this is a number that continues to increase steadily. This growth reflects sponsors' desires to contain higher development costs for biologics, which exceed those of the average small-molecule drug by about \$400 million.^{4,6,9}

To successfully navigate the clinical supply chain hurdles in both of these countries requires significant effort, including effective communication, clear identification of roles and responsibilities, a keen understanding of the local and regulatory environment, and the ability to generate customisable solutions in an environment of rapid-fire change.

China: Top Off-shore Clinical Trial Site

A 2007 survey by A.T. Kearney ranked China as the "most attractive" off-shore clinical trial location for several key reasons, among them the ability to rapidly recruit patients and the low costs of conducting studies.³

Chinese physicians enroll virtually all subjects into clinical trials, as compared to their American counterparts, who recruit only about a third. Insufficient numbers of patients is a key reason why 86% of US trials are delayed a year on average. In addition, the average grant to a Chinese primary investigator is a modest \$1,000, excluding an additional \$2,000 for laboratory testing, making Chinese clinical trials among the most cost-effective in the world.^{4,6}

Ease of patient recruitment and low costs are not the sole incentives for conducting clinical trials in China, however. The Chinese government

nation of 1.3 billion potential patients.^{4,6}

Balancing a rich source of potential patients and low costs are the considerable challenges of conducting trials in China. Bureaucracy is one of the most formidable hurdles to overcome in a country where jurisdictional disputes over paperwork can delay shipments of temperature-sensitive materials: it can take as much as a year for permission to begin a trial and any change in drug sourcing can require an entirely new submission to the regulatory body.^{4,6}

The Chinese government also requires quality testing of investigational drugs prior to the start of a clinical trial, although the government body responsible for the testing - the National Institute for Control of Pharmaceutical & Biological Products (NICPBP) – may lack the necessary facilities or tools for conducting such analyses.^{4,6}

Best Practices in China

Stay current on drug regulations, which are frequently described as a moving target: The complex tier of policies and regulations by national, regional, and local government authorities regarding the import and use of study drugs can lead to jurisdictional disputes, such as a refusal by regional authorities to recognise drug import licenses issued by national authorities. Such issues with shipments of drugs or accompanying paperwork may cause prolonged and costly delays in customs, with all the hazards of temperature excursions and loss of viable drugs. A regularly updated central database of import/export, tax and duty regulations sourced globally enables Fisher Clinical Services to avoid such delays by staying on top of evolving policies and regulations.^{4,6}

Be knowledgeable about the local and regulatory environment: Navigating the regulatory environment efficiently is another key challenge of conducting Chinese clinical trials; doing so effectively can aid in planning by saving time and resources.^{4,6}

Minimise ethics and contamination concerns through professional management of the supply chain: A high standard of control in dosage manufacturing and packaging assembly is essential, along with thorough and complete accompanying documentation. Compliance with Good Distribution Practice (GDP) during the movement of the Investigational Medicinal Product ensures that material integrity and efficacy are uncompromised. It is also extremely important to work closely with the clinical sites to ensure that storage locations are controlled and secure, particularly with respect to temperature-controlled drugs.

Use centralised and regional distribution centers for clinical trial materials: Doing so improves distribution and logistics efficiencies and limits the times when trial drugs must pass through customs.

Europe, for instance, can take a long time to arrive and even more time to be processed once they land in China.

Maintain a 12-month remaining shelf-life at drug import: Long shelf-life of trial drugs provides the flexibility necessary to wait out the time until a trial start is approved, as well as unanticipated delays, should there be customs or other causes for trials to start late.

'Ring fence' China trial drug stock in IVRS once the Clinical Trial Approval (CTA) is in place: Segregating trial drugs intended for China and using a web-based, interactive voice response system to monitor supply ensures that a sufficient inventory of pre-cleared trial drug is maintained. That is critical in a country where multiple sourcing of trial drugs is not permitted.

Use a courier company with a local presence to manage the customs clearance, which can be time-consuming: Ground handling on arrival is critical and can be a vulnerable point in the clinical supply chain. Careful management is particularly important when handling temperature-sensitive materials. Using performance metrics to select the right premium courier companies can go a long way to ensuring reliable, on-time delivery.

Be aware of China's many holidays, which can cause delays: China has 16 legal holidays, some of which are celebrated over several days. In addition to the fact that the Chinese don't work on these holidays, several of the celebrations, such as National Day in October, are times of peak travel within the country.¹⁰

Learn the language and how to read between the lines: A high level of cultural courtesy means that the Chinese typically find it difficult to say no, so knowing the language and being able to interpret what is actually being communicated is essential. Fisher Clinical Services has a Beijing office staffed entirely by Chinese employees, which helps the company manage communication barriers in a country where the official language of Mandarin is spoken alongside thousands of dialects.¹¹

Establish good relationships: Close contacts are important in China, where knowing and liking someone often means smoother business transactions, so establishing positive relationships with clinical investigators and state-run hospitals is critical.

India: Number Two and Growing

India, ranked as the second most attractive off-shore location for clinical trials in 2007, owes its transformation into a global hub of drug testing to the advantages of time, people, and low cost.^{3,7,9}

Unlike China, where approval to start a clinical trial demands months of patient waiting, India has a 12-week study start approval process. With a population of 1.1 billion, India also has a large treatment-naïve patient pool with a combination of tropical diseases and the chronic conditions common in the industrial world, enabling quick trial recruitment. Many Indian physicians who received their medical training in the United States or Europe now work in well-equipped, tertiary-care hospitals where English is the language used for documentation and medical communication. Finally, the cost to conduct an Indian clinical trial for a standard drug is 60% less than the \$150 million price tag in the United States.^{3,7,9}

That is not to say, however, that conducting clinical trials in India is without its disadvantages. Like China, concerns about safety and ethics

2006 during clinical trials conducted at the government-owned All-India Institute of Medical Sciences (AIMS).¹²

In addition, local experience in conducting trials is limited, knowledge of Good Manufacturing Practices (GMP) at trial sites is variable, and Indian logistics service providers are not yet equipped with the infrastructure to handle the large volumes and diverse distribution networks needed by pharmaceutical sponsors. The challenging Indian climate is another hurdle, since biologics must be held and transported in the cold chain and monitoring is crucial to ensure proper temperature throughout storage and shipment. GMP-compliant facilities, with a full suite of analytical services, are required in order to evaluate whether a biologic product is stable or has changed during transport or storage.^{3,7,9}

Further, there is greater possibility of record-keeping error in India since the country's information technology (IT) infrastructure is based on manual systems and is yet to advance beyond phone/web support to next-generation technologies, such as radio-frequency identification (RFID) chips and global positioning system (GPS) tracking devices.^{3,7,9}

Finally, intellectual property (IP) protection in India has historically lagged, though improvement came with the 2005 signing by India of the World Trade Organization's (WTO) Trade-Related Aspects of Intellectual Property Rights (TRIPS) agreement. The TRIPS agreement excludes patentability for derivatives of known substances unless it is proved that the efficacy is significantly greater than the original substance. This lack of guaranteed protection leaves some international sponsors with lingering IP concerns.^{3,7,8,9}

Best Practices in India

As in China, having local knowledge in India is essential: Local offices can play an important role in keeping track of the changing landscape. Fisher Clinical Services has two offices in India, a Bangalore distribution facility for drugs and other clinical trial materials, and a new facility in Ahmadabad for packaging and labeling raw drugs to produce patient kits for trial sites. Fisher Clinical Services is the first company to open a drug packaging facility in India.

Understand the rules regarding documentation, especially with respect to labeling: Written in English, labels are required to bear the drug name with strength, batch number, expiration date, protocol number, storage condition, address of manufacturer, be marked for clinical trial use only, and include cautions and directions for use based upon the protocol. It is also important to understand which documents are required for import license applications and for imports because, like China, customs delays in India are commonplace. Knowing site or location-specific requirements, such as those for trial sites in West Bengal where state import requirements differ, is also necessary. Finally, it is worth noting that these requirements may evolve and change over time, so it is critical to keep careful track.

Consider a centralised distribution strategy: A regionalised "hub" approach provides flexibility in shifting drugs to support actual trial enrollment rather than a more restrictive country-specific approach. Some countries may benefit from a local drug repository, located in country, to avoid risk of delay with regulatory approvals. Movement of drugs, and indeed packaging assembly, in Special Economic Zones (SEZs) does not require such regulatory approval, hence the drug can be packaged and ready to ship in country immediately upon license approval, a significant time and cost-saver. Finally, all depots are not created equal - prior validation of capabilities is critical, particularly for those that receive and store temperature-controlled clinical trial

Finally, keep the following in mind when conducting trials in India:

- Duration of regulatory approval can vary dramatically
- Direct-to-site shipments from a centralised facility outside of India or China can become impractical
- Novice staff at the clinical trial sites themselves may be new to requirements for receiving and returning investigative drugs, requiring additional training

As clinical trials conducted in China and India continue to grow in number and complexity, Fisher Clinical Services will maintain its focus on managing change on behalf of its global pharmaceutical customers. As one manager put it, "Our goal is to look after the interests of drug sponsors from a quality and cost perspective and to guide our customers carefully along this journey" ■

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