

White Paper

Navigating the Clinical Trial Supply Route in China

Assuring Integrity from Start to Finish

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Introduction

Inceptua has been actively operating in China for almost 20 years and is continuing to expand capabilities throughout the APAC region. Our office in Shanghai is where our specialist China team is based, supported by our extensive teams in Europe and the US. Therefore, Inceptua is well positioned to deliver high quality products and services compliant with the ever-developing regulatory landscape in China.

In this paper we will explore all of the possible pitfalls facing sponsors in more detail and offer some strategic solutions, helping you to understand and mitigate the risks, thereby ensuring successful results in your clinical trial program.

Background - the clinical trial sector in China

China is soon to become the world's second-largest pharmaceutical market, surpassing Japan. China's senior population is growing, and a more modern lifestyle combined with a better overall health lead to longer life expectations but simultaneously illnesses like heart disease and diabetes are on the rise. Environmental pollution from industry and urbanization has also contributed to rapidly differing disease patterns, with proven links to increases in cancer. This offers opportunities for innovative pharmaceutical and biotechnology companies to enter the market. To access this market and to understand the specificities raises several challenges for Western sponsors in China - regulatory, operational, cultural, and infrastructural challenges being at the forefront.

In response to the knowledge that the challenges within this sector are substantial, the Chinese government has, over recent years, introduced several measures to remove some of the major obstacles.

In line with the government's desire to modernize and improve a wide range of regulations, as well as to more closely align with established regulatory systems in the rest of the world, the major reforms are expected to have a positive impact on China's healthcare system, and the wider pharmaceutical and biotech industry. Further reforms, with associated legislative and regulatory updates, can be anticipated.

"Made in China 2025" is the Chinese government's plan to create a 'modern', more globally competitive economy. The aim is to transition away from older industries, such as coal and steel, to make way for higher value industries, focused on science and innovation.

Amongst the '10 key sectors' targeted by the Chinese government are 'pharmaceutical' and 'medical devices'. A clear goal is to make Chinese biopharma companies more competitive, and to have Chinese firms move up the value-added chain in production.

Ref (1) <https://themedicinemaker.com/manufacture/make-china-great-again>

Even though there have been approximately 20 years of exposure to globalization in the pharmaceutical sector, overcoming supply chain hurdles still requires a strategic approach. Sourcing comparator drugs is costly. Building a trusted supply route in unfamiliar parts of the world is a challenge, but a necessity. There is a need to address the quality, safety, and efficacy of imported comparator products, and there is a need to ensure the integrity of the source.

Regulatory updates from China NMPA

The China Food and Drug Administration (CFDA), now NMPA, is the administrative body responsible for the regulation of medical devices and pharmaceuticals on the Chinese mainland. Please note: this white paper will make reference to both the CFDA and the NMPA as interchangeable.

“On October 8, 2017, China’s State Council proposed new regulations for drugs and devices. Although these regulations have not yet taken effect as laws, the proposed changes include:

- Acceptance of foreign clinical trial data for drugs and devices, which should reduce the need for local clinical trials in China. The global trials must be conducted at multiple centers and the data must meet the NMPA’s regulatory standards.
- Removal of the certification system for medical institutions certified to conduct clinical trials; instead, manufacturers will be responsible for recruiting third parties to conduct trials.”

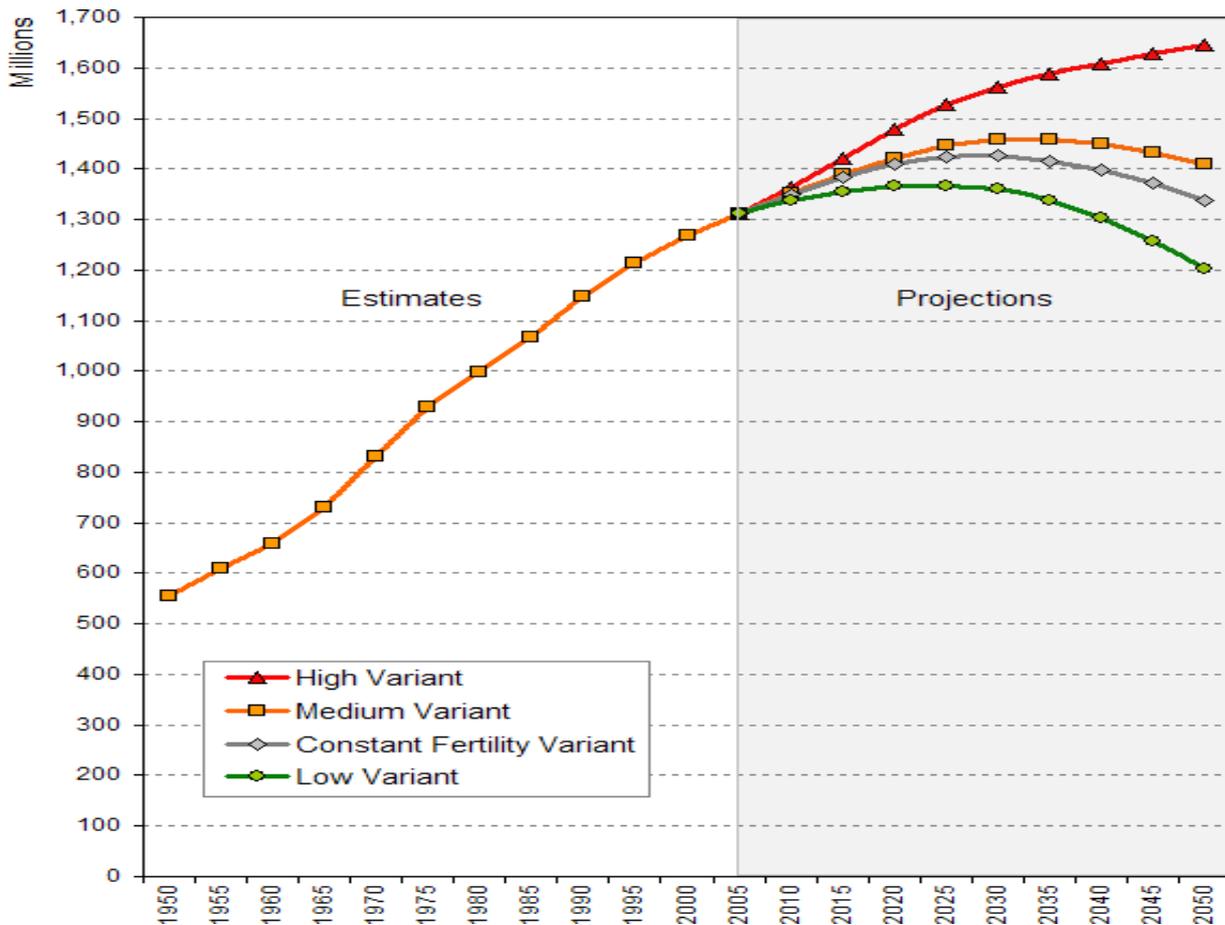
Ref (2) New Chinese Drug and Device Regulations October 8th, 2017

The above proposals could positively impact the domestic clinical trial sector in China.

What is driving the clinical trial market in China?

China carries approximately 20% of the world’s population, with a growing similarity to the Western world with regard to the patterns of morbidity and mortality. Therefore, China’s potential to recruit a sufficient number of trial subjects is enticing for global pharmaceutical manufacturers and local biotechnology companies alike.

There is an expanding appetite for conducting clinical trials in China, primarily driven by perceived reduced costs, and access to a large treatment naïve patient pool. In 2017, 241 million people in China were over the age of 60, by 2050 this figure is expected to grow to 487 million people. One of the more significant changes is that foreign data is being accepted for registration as long as there is no ethnic difference in the patient population.



Graphic 1: A significantly growing Chinese population in China. In Song, Xingqiang & Wennersten, Ronald & Mulder, Karel. (2007).

The graphic representation above demonstrates that the population is predicted to grow significantly and clearly leads the assumption that the overall population growth will guarantee the ageing population will be an integral part of future clinical studies demand.

Another improvement is that significant regulatory changes have been implemented to close the gap for NDA approval. “ICH” guidelines have been adopted and the CTA approval process has been shortened to 60 working days.

Dr. Lingshi Tan stated in Pharmaceutical Executive in February 2019
Volume 39, Issue 2 Feb 19, 2019:

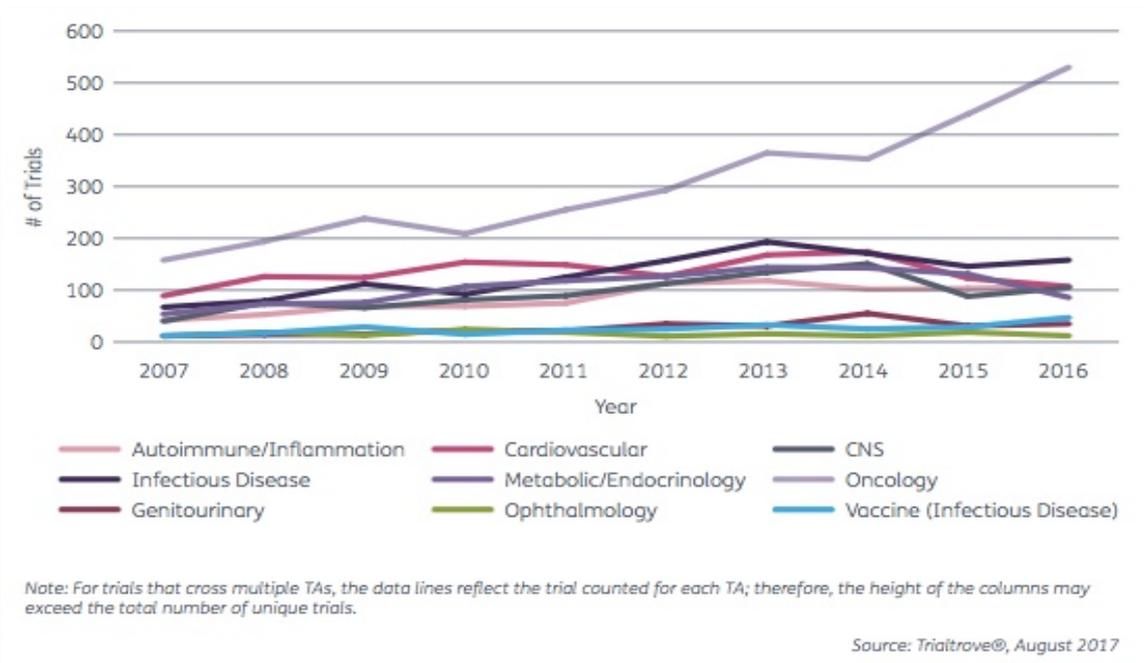
“As ICH guidelines become China’s standard, China is increasingly willing to accept global clinical data in support of local product registrations, with priority for products that serve Chinese patients’ unmet medical needs. In fact, in August of last year, the NMPA specifically asked biopharma firms to register 48 foreign drugs that had not yet been introduced in China and demonstrated its willingness to speed up approvals using global data.”

Region	# Studies in 2018
China	401
Thailand	53
S. Korea	339
Japan	275
Singapore	66
Australia/New Zealand	368

Table 1: Clinical trial studies conducted in 2018. Source: Clinicaltrials.gov

Selection Criteria: Industry sponsored, intervention studies in East Asia, Southeast Asia, Asia Pacific, Japan, Early Phase I-III, start date 1/1/18–21/31/18 (May 2019)

China has historically offered a large homogenous population. This, coupled with a rapid economic growth and an increasing interest by the government to invest in research and development, has resulted in several hundred research organizations in China. As mentioned above, the regulatory framework is starting to match the FDA structure. Finally, the Chinese government’s Five-Year Plan has pledged to dedicate 18 billion USD into research and development.

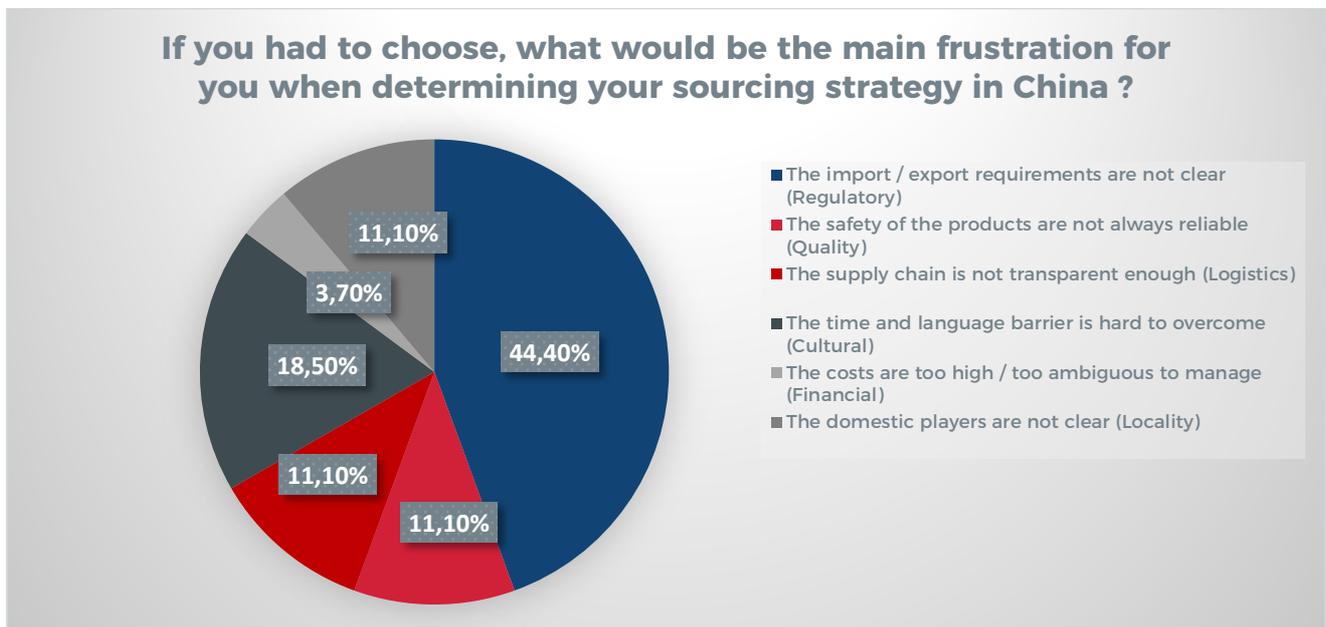


Graphic 2: Clinical Trials: A Preview of Upcoming Clinical Trials in 2019, Reference Global Data; Code: GDHC2194EI, Figure 3

The leading therapeutic areas in clinical trials are starting to mirror the disease profiles prevalent in the Western world. This chart shows the projected growth of the prevalent diseases.

Collective concerns - clarity and integrity

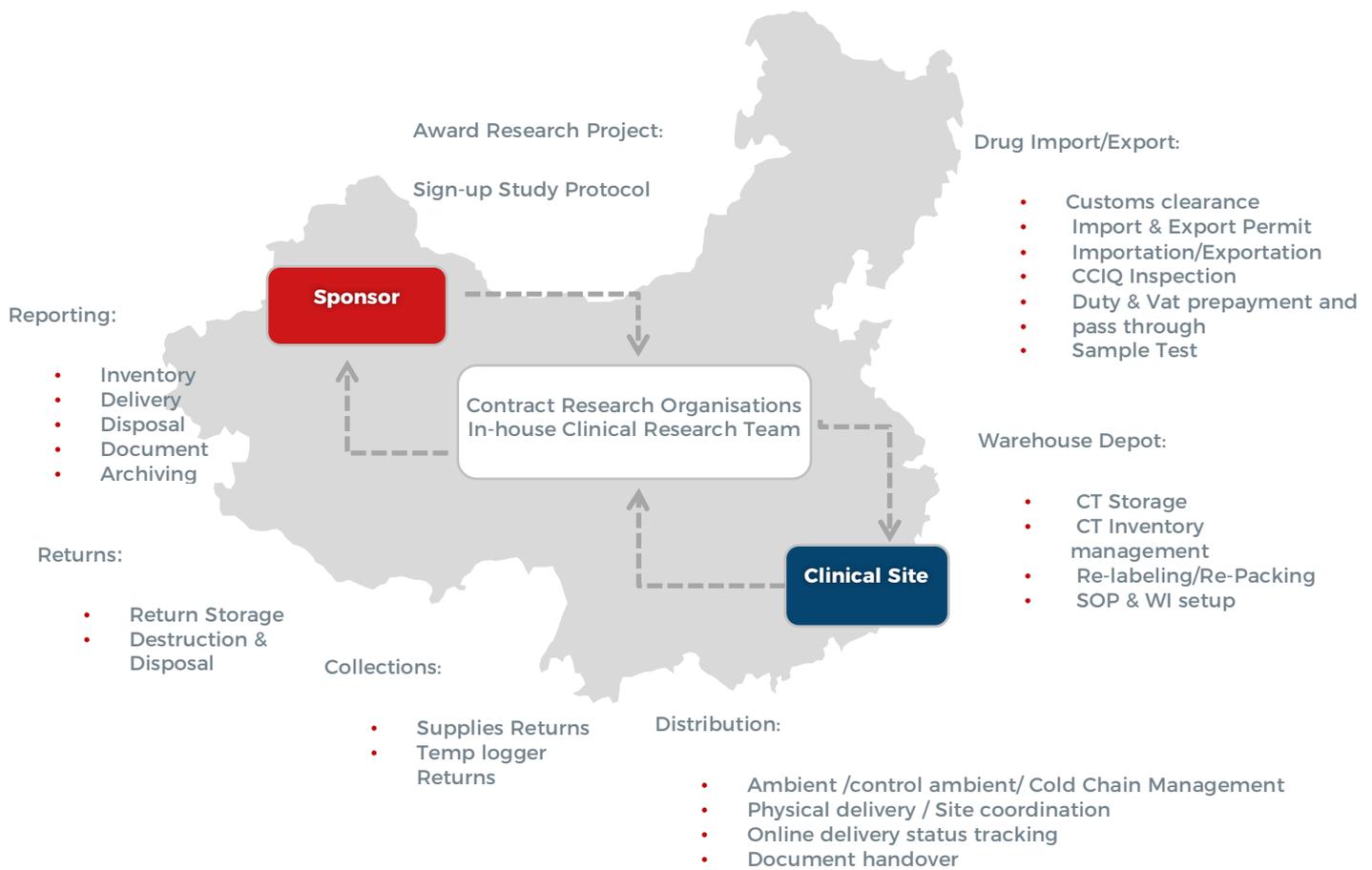
Inceptua’s customers have recently reported their concerns to us as part of a survey. Problems reported include navigating the cultural differences, ensuring the integrity of the sourced material, and the integrity of the supply chain, but overwhelmingly it is the lack of clarity around the required documentation that proves to be the most challenging. In addition, it is imperative to note that regional differences within Chinese culture can stretch the understanding of Western organizations.



Graphic 3: Main frustrations for non-Chinese companies in China. Source: Inceptua Survey from April 2019, #50 participants

Choosing reliable sourcing specialists, guarding the integrity of the supply chain, managing evolving regulatory requirements, and transporting temperature-sensitive drugs in vastly varying climates are all complex and time consuming.

It will be increasingly difficult to conduct a successful clinical trial program without partnering with an efficient, knowledgeable supplier who is confident in delivering a secure and compliant supply chain.



Graphic 4: Example of clinical manufacturing steps in China. Source: Inceptua

The pitfalls can be mitigated by the choice of supplier. It is necessary to partner with a company familiar with taking a strategic approach, one that considers all aspects of the requirements in the preliminary phase and customizes the methodology to the particular market – preferably whilst the protocol is in development.

It is important to choose a partner who has an extended network in the region capable of procuring material direct from source in order to mitigate the risk of compromising the integrity of the study by receiving counterfeit products into the supply chain.

Choosing a supplier who has the capability to assure the integrity of the supply chain from the very beginning - from procurement through the warehousing steps and logistics service - is essential.

Furthermore, it is critical to choose a supplier who has a GMP License Accreditation in China.

Assuring integrity in the quality of your supplier

Navigating the supply chain relationship – it all starts here.

It is highly recommended to partner with suppliers in emerging markets like China who clearly meet the same US FDA and European Union quality standards or requirements.

Specific reference is made to the required standards from the supplier, warehousing, and shipping partners as this will impact on the integrity of the trial, the outcome of the trial, and the subsequent commercial value of the trial.

When deciding on the choice of partner several questions should be addressed:

- 1) How accessible is the required reference product directly from the manufacturer?

If the supply chain is long and complicated it will potentially open up the possible receipt of counterfeit product – drug counterfeiting is a proliferating worldwide problem that affects both developed and developing countries. Over the past few years, an increasing number of counterfeits have been observed, with China being a major source. The WHO has estimated that up to 30% of drugs sold in parts of Asia, Africa, and Latin America are counterfeit.

- 2) How can I be reassured of the integrity of the production standards and differences?

Unfortunately, possibly due to a lack of understanding generally, some suppliers may not consistently adhere to temperature controls for cold chain products during storage and transportation. This can often be a necessary concern to sponsors and efforts must be made to avoid this happening. Partnering with an experienced provider who has the capacity to offer a bespoke, quality assured process from procurement through to delivery is an aspiration for most sponsors – but essential. On occasion, we have intercepted products which have failed our own robust quality checks. Below is a clear example (insect in sealed packaging) of failing standards in production and quality, one which we managed to prevent entering the supply chain.



Picture: Example of inferior quality packaging. Source: Inceptua, internal quality checks

Inceptua's comprehensive quality overview guarantees GMP conformity throughout the clinical supply chain. Meeting the high expectations of our customers and ensuring our adherence to regulations in all regions is the core of our business. Our aim is to maintain close communication routes throughout the duration of the trial, allowing us to respond with flexible solutions, whilst keeping track of your costs.

3) What documents should be supplied to guarantee importation is successful?

We know that the most important single document for importation is the Import Permit issued by one of the provincial and municipal drug authorities, for example the Beijing Food & Drug Administration (now known as the Beijing NMPA). Once the application has been made through the chosen port, then all arrangements should be made to import through that authority rather than another port

Together with the permit, the following documents must be presented for customs clearance to take place:

- Customs Invoice
- Copy of the airline paperwork (the Master Air Way Bill)
- Packing List
- Certificate of Analysis (or Certificate of Origin, depending on the port of entry)
- Clinical Trial Approval which comes from the consignee together with a copy of their business license,
- First Leg Document showing the batch / lot number as indicated on the invoice.

There are many requirements for the customs invoice including the shipper and consignee's name, address, what the contents are, shipment commodity description, country of origin, expiry date, batch number, manufacturer company name and shipper company name. Every single one of these must match the same details on the inner packaging label on the packages. Any discrepancies could lead to delays at customs and the China Inspection & Quarantine.

4) What cultural differences must be considered?

“Guanxi” or relationship building is a system of social networking. Because of the importance of Guanxi, after work activities are commonplace in China - the Western approach of not mixing business with pleasure often does not apply in China. So, understanding the culture of hospitality is integral to business success, as is adopting the correct business attire. Finally, remember that an established culture in Shanghai or Beijing may not necessarily apply in the inner regions of China at all.

Assuring integrity in your warehouse

Today's warehouse and distribution market within China is complex and challenging, however it is generally believed that the status quo will change as distributors continue to consolidate.

The central government's 12th Five-Year Plan (for 2011-2015) called for the establishment of one to three national distributors with sales over 100 billion yuan (\$15.6 billion) and 20 regional distributors with sales over 10 billion yuan (\$1.6 billion). This consolidation has already begun, with Sinopharm making more than 30 acquisitions in 2010 and 2011 alone. Beyond this acquisition surge, local regulators are tightening drug distribution license issuances and renewals, forcing small and less qualified players to exit.

How to mitigate the risks

A qualified pharmaceutical wholesaler must:

Employ qualified pharmaceutical professionals, including licensed pharmacists; and possess the necessary premises, equipment, warehouse, and a hygienic environment for drug distribution.

They must operate an independent computerized information system that monitors the purchase, storage, sale, and distribution of pharmaceuticals and record quality control activities.

Compliant facilities must set up premises, office buildings, warehouse management, quality control, and safety safeguards in the warehouse, and maintain the warehouse in a compliant manner. Finally, facilities must implement internal rules and policies to ensure the quality of drugs that it distributes.

Checklist for assured integrity of manufacturing facility and supplier

- Open a strategic partnership with a manufacturer with many years of experience in clinical manufacturing services; it is critical to choose a GMP certified facility.
- Choose a warehouse situated close to good transport links, i.e. close to a major airport.
- As part of the quality audit, ensure that the warehouse has an excellent infrastructure, including good pest control.
- Ensure the warehouse offers exclusive storage areas for both cold chain and ambient material.
- Check the warehousing partner holds the appropriate licenses and that it abides by global GDP standards.
- Ask for sight of the SOP's which demonstrate staff are all highly trained with particular emphasis on Operations and Maintenance standards.
- Look for evidence for high level quality control with fastidious attention to detail to checking both goods in and goods out procedures.
- The license is valid for 5 years, so make sure your supplier conducts regular audits.

Assuring integrity in your logistics

China requires extra attention to detail to ensure that everything is in place for the seamless shipping, clearance, and storage necessary for successful supply to investigators and ultimately to trial sites. Be aware that risk exists throughout the whole supply chain, including the manufacturing stage, through the transport, warehousing, relabeling, and eventual distribution to the clinical trial sites. There is no shortcut!

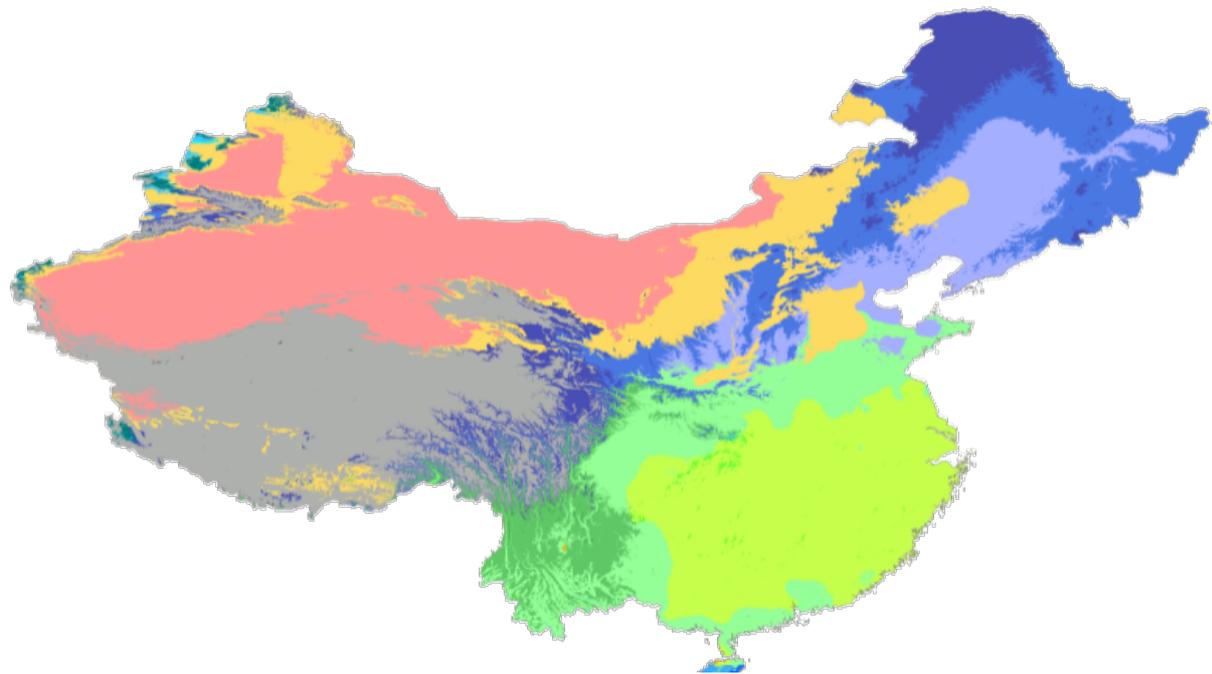
The logistics supplier's qualification process should include robust risk assessments of their own practices. Criteria should also evaluate the reputation and referrals, licenses, capacity, pricing, economic status, and financial stability.

Our warehouse partner in China is aligned with EU GDP guidelines, and the Inceptua globally harmonized SOP's ensure that the warehouse individually inspects goods in and goods out. This is a very important factor to consider when evaluating your complete clinical trial supply strategy in China.

How to mitigate the risks

Partner with an established logistics supplier, which should be increasingly possible because supply chain capabilities are growing. Inceptua has partnered with global providers with decades of experience in the Asian market. However, be cognizant of the challenges the logistics provider faces in the huge variables in infrastructure once out of the coastal developed areas such as Shanghai.

In addition, it is important to recognize that China's geography is marked by both vast altitudinal and latitudinal spans with the resulting variances in climate. Thus, safely monitoring and recording cold chain shipments in a predictable manner is a challenge - the last mile delivery often presents the greatest problem. Perhaps the most singular way to mitigate risk is to always implement a secure solid insurance scheme, especially for large and valuable shipments.



- | | | |
|--|---|--|
| ■ Am (Monsoon) | ■ Cwb (Subtropical highland) | ■ Dwc (Dry-winter subarctic) |
| ■ Aw (Savanna) | ■ Cwc (Cold-summer subtropical highland) | ■ Dfa (Hot-summer humid continental) |
| ■ BWk (Cold desert) | ■ Cfa (Humid subtropical) | ■ Dfb (Warm-summer humid continental) |
| ■ BSh (Hot semi-arid) | ■ Cfb (Oceanic) | ■ Dfc (Subarctic) |
| ■ BSk (Cold semi-arid) | ■ Dwa (Hot-summer continental) | ■ ET (Tundra) |
| ■ Cwa (Dry-winter subtropical) | ■ Dwb (Warm-summer continental) | ■ EF (Ice-cap) |

**Isotherm used to separate temperate (C) and continental (D) climates is -3°C
Data source: Climate types calculated from data from WorldClim.org*

Graphic 5: Climate types of China. Source: (Ref 7) Adam Peterson - Own work, CC BY-SA 4.0, <https://commons.wikimedia.org/w/index.php?curid=52784541>

Checklist for assured integrity in your logistics provider

- Logistics are definitely the potential principal pain point.
- Ensure the licenses and certifications are valid, and regularly audit the service.
- Inceptua only partners with logistics providers who always provide us with temperature maps, and always use double temperature monitoring processes.
- Inceptua only partners with expert, qualified, bespoke freight companies with detailed knowledge of how to navigate customs clearance requirements.
- It is imperative to only work those providers who are experienced in obtaining the documentation required by customs officials.
- Check for the option of running test shipments for clients' clinical trial material, with the objective of exposing any weak links in the supply chain.

Summary

It is clear that China is quickly becoming a clinical research center due to the availability of a vast, treatment-naive patient pool. Many diseases are now starting to display both the rate of incidence and type prevalent in the Western world.

Government spending on healthcare in Asian countries is relatively low compared to the US and Europe, so patients' willingness to enter clinical trials helps them to gain cost-free access to innovative therapies.

Pharmaceutical and biotech companies should look to partner with distributors who offer full-service logistic solutions in order to control their supply chain more effectively and reduce possible risks in their supply chain. Early-stage consulting, reliable access to products, and a full-service logistic solution will provide an according foundation for non-Chinese companies to be successful and make the most of China's opportunities.

Pharmaceutical and biotech companies should look to partner with distributors who offer full-service sourcing and logistic solutions in order to control their supply chain more effectively and reduce possible risks.

Inceptua's long heritage in the Clinical Trial Supply area within Asia will provide sponsors with a trustworthy service.

Inceptua has an established infrastructure in China, benefitting from an amalgamation of both native Chinese employees and Chinese speaking Western personnel, thus offering sponsors the highest level of service for sponsors who are planning to run clinical trials in China.

A specific focus overall for Inceptua is Asia, where Inceptua has had a footprint since launching a Japanese office in 2010.

Our Executive Vice President, Kay-Christian Karstadt has over 20 years' experience of clinical trial supply operations in Asia. In addition, the other dedicated members of the Asia team also contribute to ensuring successful collaborations between East and West.

Inceptua has recently been awarded the TOP 10 Clinical Trial Services supplier 2019 by Pharma magazine, Tech Outlook.

References

Ref (1) <https://themedicinemaker.com/manufacture/make-china-great-again>

Ref (2) New Chinese Drug and Device Regulations October 8th, 2017

Ref (3) http://www.nmpa.gov.cn/WS04/CL2077/300629_9.html

Graphics

Graphic 1: Challenges of Sustainable Development in China Song, Xingqiang & Wennersten, Ronald & Mulder, Karel. (2007).

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Tables

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Pictures

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