Setting the Standard for Central Labs in Asia Pacific and China

PEER REVIEWED

For more than two decades, central laboratories have been an important part of running global and large multi-regional clinical trials in Europe and the United States. With the rapid increase in the number of global clinical trials in China and the Asia Pacific region, trial sponsors should understand how to choose central labs in those regions, and the reasons for those choices. This article focuses on Singapore and China. Although Singapore has emerged as the hub for central labs in the Asia Pacific region, trial sponsors will continue to need a separate central lab in China, and must understand how these labs need to be set up there.

Historical Perspective: The Development of Central Labs in the West and the Growth of Clinical Trials

The concept of the central laboratory originated in the United States, and was related to the hospital diagnostics business when Metropolitan Pathology Laboratories was founded in 1967. The company changed its name to MetPath in 1969, was acquired by Dow Corning in 1986, and spun off as Quest Diagnostics in 1997. Improved automation in the laboratory along with better IT systems enabled the central lab concept to develop, and the model was adopted in Europe in the 1980s and in the Far East in the 1990s to support clinical trials analysis.

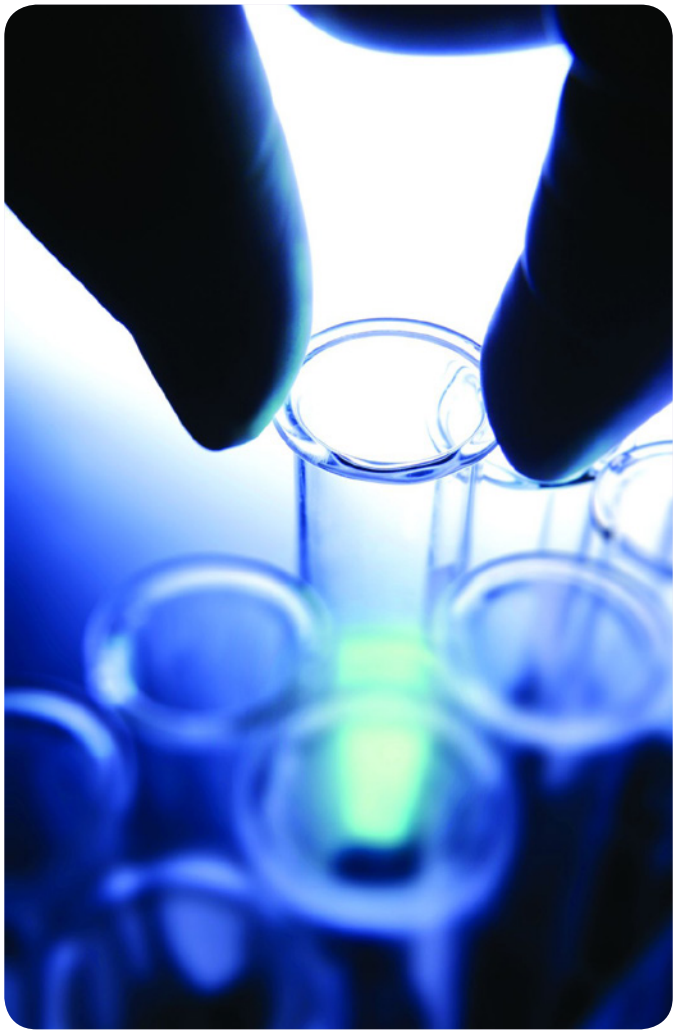
The MetPath concept entailed the analysis of large quantities of samples in strategically placed locations near to communications hubs. This enabled transport of samples to central locations within short sample stability timelines. The business was driven by the private United States health sector and coincided with the development of improved air transport infrastructures led by FedEx, and better IT capabilities enabling rapid results delivery and flexible reporting capabilities. The outcome was economy of scale and lower cost.

The central laboratory concept in the diagnostic world was then adapted for clinical trials. In this model, samples from each continent and all the laboratories in the network are consolidated, and data is entered into a single database. This is possible because these data came from similar instrument platforms, meaning that they can be harmonised. Before the central laboratory industry was established, local laboratories near to trial centres, or laboratories preferred by sponsors or investigators would be used.

The challenges of handling multiple reference ranges, variable quality standards and the management of large numbers of laboratories became nearly impossible for large Phase III trials. Improvements in global availability of the same instrumentation, better harmonisation of methods, and the expansion of airport networks made it possible for central laboratories to support global trials.

The Establishment and Operation of Central Labs in Asia Pacific

As more pharmaceutical companies have been expanding their research activity in Asia Pacific, the clinical trial support network in the region has improved. While the number of clinical trials conducted in the United States declined 12 per cent from 2009 to 2012, the number of clinical trials increased 24 per cent in developed Asia Pacific nations, and 18 per cent of developing Asia Pacific nations during the same time period. During that same time period, the number of clinical trials in the Asia Pacific region, excluding Japan and India, grew from 250 to 475. In the United States, growth was slower, with 6656 trials in 2007 compared to 7616 in 2012 [1].



Just as the expansion of clinical trials in the United States drove the development of the central labs industry, the increase in the number of global trials in Asia Pacific has spurred the establishment of central labs in the region. Throughout Asia Pacific, many central labs have been set up as wholly-owned entities, rather than as partnerships or independent subsidiaries, as this structure allows for the

use of consistent operations standards around the world. Singapore has emerged as the chosen hub for central labs in the region.

A hybrid central lab business model also emerged. This model provided central laboratories with their own facilities in the United States and Europe to use third-party laboratories in the rest of the world to procure global multi-centre trials. In addition, there are CROs or organisations without their own labs, but who partner with third-party labs globally. All types of global central laboratory strategies have their advantages and disadvantages. Historically, central labs initially partner with a regional lab when entering a foreign market until sufficient business warrants the investment to build their own lab facilities. This wholly-owned central lab model provides advantages that include data integrity, homogenous data integration, and functional controls. Even with the advantages a central lab offers over other models, there still may be the need to partner with regional labs to outsource esoteric tests. Other aspects to consider in retaining partnerships with regional labs are expertise regarding logistics, and navigation of regulatory guidelines.

The operational hybrid approach allows sponsors to take advantage of established, regional central labs while benefiting from advanced data management systems for the centralisation and harmonisation of test data.

In addition to the global central labs, there are local diagnostic laboratories that play various pivotal roles in clinical trials. They are involved in almost all the Phase I and IV testing, and some speciality testing. Up until the early 2000s, local diagnostic labs in Singapore conducted at least 60 per cent of clinical trial testing, according to local experts active in the industry at that time. Though these local labs provide very high-quality results, they cannot provide services such as logistics and project management. Today, more than 80 per cent of clinical trials in Singapore are coordinated through central labs, these local experts report. Although local diagnostic laboratories still play a minor role, they are conducting some of the esoteric, low-volume but high-margin testing. Additionally, most non-time-critical esoteric tests can be consolidated in Singapore and shipped to the United States, a European parent laboratory, or specialised laboratories.

Considerations for Selecting a Global Central Lab Partner for Asia Pacific Trials

All central laboratories are able to provide testing, specimen management, data management, project management, logistics management, and kit production. For trial sponsors, the critical factors in deciding which central lab to use are competitive price, a broad test menu that includes speciality testing, global reach, logistics management, flexibility, proactive communication, an extensive customer base, and industry reputation. Other considerations for choosing a central lab in the region are an expert staff with extensive clinical trials experience, local knowledge of regulatory requirements and country-specific logistics, and familiarity with local customs and languages.

The competitive advantages that large central labs often have over smaller labs are economies of scale, such as having a broader test menu and more expertise. Pricing of a test and construction of a full-service proposal can be done in many ways, however sponsors may not be able to compare services directly on a like-for-like basis.

The same applies for logistics costs, where pricing can vary based on whether the transportation company considers a city to be primary, secondary, or tertiary in its network. The logistics costs in Asia Pacific can be two to five times more expensive than the United States. Additionally, the primary logistics service providers in the region are not the same companies as those found in the United States, which means having to establish trusted relationships with new vendors. However, FedEx is expanding biomedical logistics capabilities into Asia Pacific. This concern is not specific to central labs in Asia Pacific, and can also be found in Europe and South America. Ultimately, the effective selection and management of couriers is a key requirement of the central laboratory, and global logistics experts are a very important asset to the central laboratory team.

Even though the considerations of logistics and other expenses can be daunting, trial sponsors must have access to an Asia Pacific central lab. This need is driven by facts such as the number of registered interventional studies in Asia, which have grown at an average rate of 8 per cent over the past five years. The number of similar studies in North America fell by 2 per cent. During the same period, the number of investigators in Asia grew by an average annual rate of 14 per cent, compared with 9 per cent in North America[2].

Singapore has become a favoured hub for central labs because of its strong transportation system, and having an airport that is within a seven-hour flight of all countries in the region. Another consideration in choosing Singapore for a central labs operation is the highly-educated local population, where English has been established as the official second language for education[3].

Development and Operation of Central Labs in China

With its large, treatment-naïve population, China has become an important centre for pharmaceutical development. In 2007, there were 954 clinical trials being conducted in China. As of 2012, there were 2442 [1].

In China, local diagnostic laboratories, which are government-owned and based in public hospitals, played a pivotal role in many trials in the early days in the absence of multi-national central labs. As in the West, a shift in business has occurred to private laboratories such as Kingmed, Adicon, Wuxi Apptec, Di-an and other smaller private laboratories. Tigermed CRO is the most recent example. Tigermed is the largest China-owned CRO in China and its central lab, located in Guangzhou, was given accreditation by the College of American Pathologists (CAP) in 2013. This made Guangzhou Tigermed Central Lab the first CRO central lab in mainland China.

The market segment in China's central labs consists of

standard safety; data management; logistics and courier management; kit production; project management; integrated database management; IT reporting and flexibility; and speciality test(s). Although China is late to start offering central lab services, the industry is expected to significantly grow in all areas of clinical trials testing, ranging from PK/PD analysis, to specialised testing such as pharmacogenetic or pharmacogenomic testing. Genostratification could be the pattern of the near future, as the pharmaceutical industry is moving more towards personalised medicine, especially in oncology. This is a very important development for labs serving the domestic Chinese market, as there are proven ethnic differences in biomarkers such as epidermal growth factor receptor (EFGR) distribution in comparison to Caucasians, particularly in non-small cell lung cancer and gastric cancer. Many large central labs already have these capabilities in their Western labs and may well consider developing them further in China.

According to ChinaBio LLC, the number of ongoing global clinical trials in China nearly tripled between 2007 and 2012 to 564 [4]. However, one of the current main hurdles that could slow the rate of increase of new clinical trials is the approval time required by the China Food and Drug Administration (CFDA), which was previously the SFDA. It is critical for sponsors to start the clinical trial application process as early as possible to avoid undue delays.

Most local laboratories will take on local trials testing, and a couple of the global multi-national central laboratories are also participating. In these cases, sponsors will find that the pricing is low, compared with pricing of similar labs outside of China. However, in China, there are progressively more principaI investigator-initiated trials, with the testing price comparable to a global trial.

Multi-national central laboratories have established their presence in China. The question is whether the reverse will happen. Currently, there are no Chinese central labs that have a presence outside China. It is possible in the future that this could change.

Although China does not allow for the import or export of biological samples – meaning that all central labs in the country support the domestic market – one company has found a way to serve outside markets. WuXi AppTec is located in Shanghai Waigaoqiao Free Trade Zone at Pudong Airport, the first free trade zone to be established in China. Because the company is not technically located in China, it can receive, and has been receiving, PK samples from outside China, as a single testing location, processing samples from the United States and Europe. Recently WuXi AppTec has also set up a central safety laboratory, also within the trade zone, which means that it can handle samples from global clinical trials outside China.

Gap Analysis of Central Laboratories in China

As China's regulations prevent the export of biological samples for testing, all samples need to be tested in China. Global central laboratories in China must therefore either outsource or perform testing in-house, depending on the anticipated return on investment. Harmonisation is always an issue and can lead to the need to import materials such as reagents. Chemicals such as these might not be available in China, either because the manufacturer has not yet filed an application for the medical device to the CFDA, or because there is no distributor in China. Either way, the difficulties of needing to import and access needed chemicals and equipment could lead to higher costs, which is passed on to the sponsor. Even if a central lab is used, trial sponsors must take into account the management and oversight needed for the lab and these requirements can be considerable.

Most pharmaceutical companies recognise CAP Accreditation as a sign of compliance to quality standards. To be accredited, one has to run the proficiency survey material supplied by CAP. Import of CAP material into China is not without its problems. There have been delays in receiving time-sensitive reagents and other testing materials. As a result, CAP now has a strategic alliance with Becton Dickinson, set up in July 2013 to handle the import of CAP-approved material[5]. This is just one example of a gap, and can apply to most material that needs to be imported into China. Earlier identification of testing needs is important if delays are to be avoided.

Another factor that has to be taken into account is that to date, local operating companies still prefer to choose local diagnostic laboratories for specialised testing related to

anatomic pathology. This is related to the availability of local experts and the inability to export samples.

One of the most important considerations in evaluating a central lab is the knowledge and experience of its personnel. Sponsors must make sure that the central lab owner has a strong local team in China that can navigate the regulatory and cultural landscape, and can train personnel to work according to the standards of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and Good Clinical Practice (GCP). Because of these considerations, the inherent costs of doing business in China are relatively high.

When it comes to the talent pool, in 2008, 51 per cent of Chinese bachelor's degrees were awarded in the science and engineering fields compared with 31 per cent in the United States[6]. In 2009 alone, more than 108,000 overseas students returned to China, an annual increase of 56.2 per cent compared with 2008[7]. This, in addition to the investment by global companies in training, will reduce any gap in the talent pool in China.

Another way to evaluate a central lab in China is the quality of the data provided and how the lab handles combining data from local labs in different geographical locations. The basic requisite is to use the same instrumentation and materials. Correlation is done in real time so that sample stability is no longer an issue. Different labs use different tools, but with the same objectives and outcomes.

Many pharmaceutical companies use preferred provider status as a right to tender, and for the selection of a central laboratory in the competitive tendering of projects. There is still an exception to this in China.

Conclusion

The dominant service providers in both the United States and Europe are the private central labs, and these are also emerging as the main players in the Asia Pacific region, followed by China.

With the improvement in ICH-GCP training and compliance, more trials will be conducted in Asia Pacific and China to speed up drug development. Most large multi-national central labs are already dominating the Asia Pacific region and China. This could help to improve the overall quality of trial data coming out of the region. In addition, due to biological sample export restriction, Chinese labs that are wholly owned by CROs will need to conduct more esoteric tests to be self-sufficient. This means Chinese central labs will be creating broader menus than central labs located in Singapore or other Asia Pacific countries, and Chinese central labs could become comparable to their parent companies. However, more China-owned private diagnostic labs could enter the clinical trial lab testing business.

There are still hurdles to overcome in establishing central labs in China but these can be addressed by putting together an experienced, local team to run these operations. For the rest of the Asia Pacific region, particularly Singapore, the major concern is the cost of logistics, as logistics companies, such as FedEx, have not expanded into Singapore. Effective courier selection and management is a key requirement of the central laboratory and global logistics experts are a very important asset to the central laboratory team.

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