CHALLENGES AND BEST PRACTICES IN SUPPORTING CLINICAL BIOANALYSIS IN CHINA

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In the rapidly evolving Chinese research and development (R&D) landscape, there are several key considerations for effectively supporting global clinical trials with regulated bioanalysis in China. This white paper discusses the current status of bioanalysis in the region, in-country support and local guidance strategies to combat potential challenges in supporting clinical bioanalysis within China.

EVALUATING THE CHINESE MARKET

Recent growth in the Chinese market has largely been driven by changing regulations and accelerated approvals. The establishment a fast-track processes and alternative regulatory paths have created greater interest from multi-national pharmaceutical companies seeking to expand development and, as a result, necessitating the demand for comprehensive bioanalytical support in China.

Approvals in China have dramatically increased, from only five in 2016, to 51 new, innovative drug approvals in 2018, and 53 in 2019 (data not shown). Importantly, among approvals there is a mix of both multinational and local companies, so the rising tide created by new regulations has lifted all boats.

When considering growth in drug development, it unsurprisingly maps to similarly rapid growth across phases, particularly since 2015 (Figure 1b). Rapid growth is expected in early phases (Pre-clinical/Phase I) to accelerate late stage trial growth in the coming years.

FIGURE 1: Growth in Chinese market, by (a) approvals, or (b) phase.
FIGURE 1a:

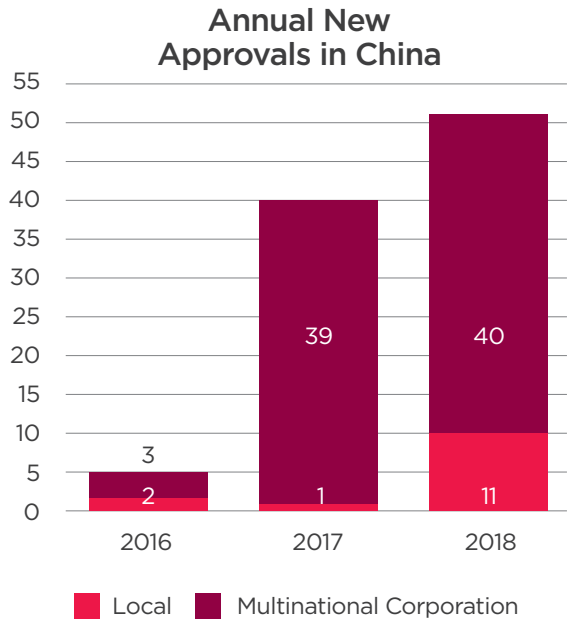
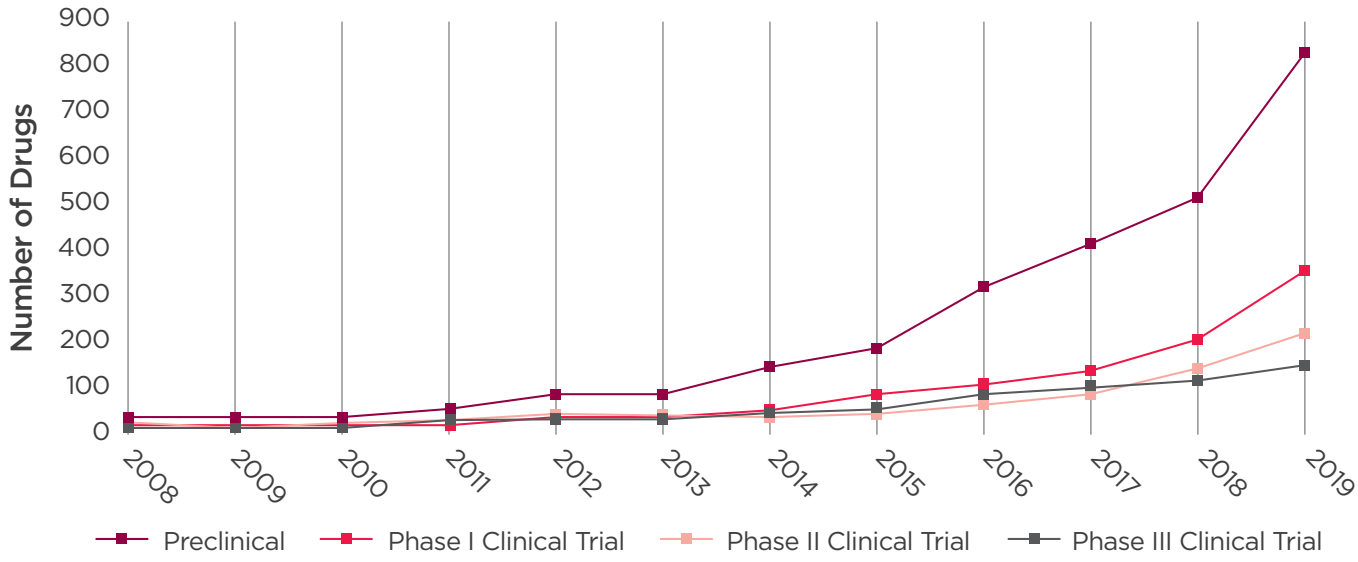


FIGURE 1b:



Sources: Deloitte LLP (2019) and PharmaProjects (2019).

LEVERAGING BREAKTHROUGHS IN REGULATORY REFORM

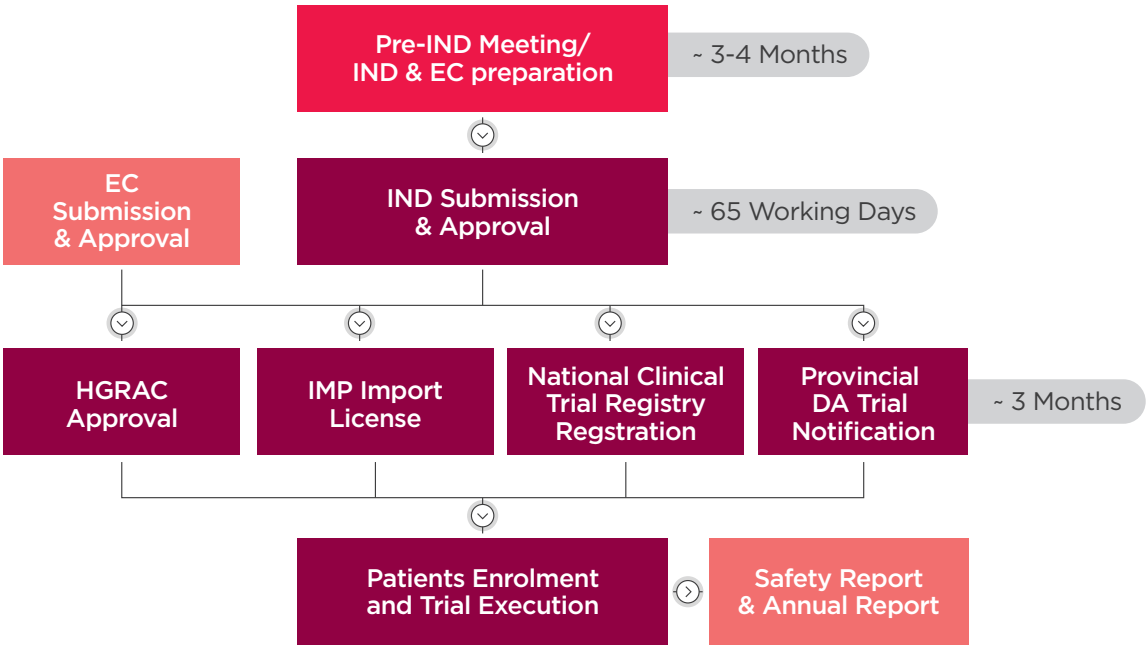
The National Medical Products Administration (NMPA; formerly known as the China Food and Drug Administration) has been engaging in significant regulatory reform over the past 10+ years. Recent market growth in the region is credited to these policy changes. The strategy has been focused on four key areas:

- Improving drug quality
- Improving review efficiency
- Encouraging drug innovation
- Improving the openness and transparency of the review process

Drug quality improvements have come out of the NMPA's broader engagement. First, NMPA policies have focused on encouraging multiregional clinical trials involving China at any stage, including Phase I. In addition, China has joined the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) which enables more rapid implementation of new, and adaption to changes in ICH guidance. There is now priority review and a fast-track approval pathway for drugs that target unmet or urgent medical needs, show obvious therapeutic advantages, or address orphan diseases. This speeds review, but also encourages innovative drug development by facilitating the review and approval of innovative drugs that have not been previously brought to market internationally.

As a result of these changes, regulatory approval has notably accelerated in the past decade. The number of approvals for new chemical entities (NCE) have had a continuous upward trend, especially downstream of 2015 regulatory changes. An increase of >35% compared to previous year can be seen in 2017 and 2018 (half-year data from the NMPA Center for Drug Evaluation). Approvals for biologics have increased even more significantly in over the same timeframe. The pharmaceutical industry has demonstrated their satisfaction with new policy changes by greater participation in the Chinese market, with >1,500 clinical trials registered annually since 2017, more than double of any previous year.

FIGURE 2: Flowchart of IND and EC approval pathways when performed in parallel.



NAVIGATING THE REGULATORY PROCESS

With many recent changes in the Chinese regulations, it's important to understand the current process from Investigational New Drug (IND)-preparation to clinical trial initiation (Figure 2). The process takes eight to ten months, if companies are comfortable obtaining ethics committee (EC) and IND approval in parallel. Pre-IND and IND preparation lasts three to four months, with the requirement that all pre-IND documents are in Chinese. The IND and EC submission and approval process lasts about two months when conducted in parallel. Once these steps are complete, national clinical trial registration, IMP import license, human genetic regulation approval (HGRAC), and trial notifications take place over three months before patient enrollment can begin.

The first key regulatory challenge of launching a clinical trial in China is that all the trials involving foreign or foreign-invested companies require HGRAC notification or approval prior to the patient enrollment. From file preparation to the final approval, this requires three months; therefore, files should be submitted immediately upon IND and EC approval. The second challenge is human sample exportation, where following HGRAC master approval trials, companies must apply for a HGRAC export permit. Once in place, this must be followed by a China Customs Bio-sample Exportation Permit Application (one to two months per shipment application) in order to navigate China Inspection and Quarantine.

These human sample exportation challenges are a major motivator for pursuing human sample bioanalysis within China, as it is dramatically more time and cost effective.

UNDERSTANDING REGULATED BIOANALYSIS GUIDANCE

There are two types of clinical studies that require regulated bioanalysis support locally in China:

- To register a new drug in China, global pharma must conduct both a PK study and a Phase III study in the Chinese population.
- China is included as part of the global trial. In this scenario, global submissions require consistent quality of bioanalysis executed in China, so it is recommended that after method transfer and validation, a cross validation be conducted to ensure comparability of data generated at different sites.

Due to the aforementioned challenges with human sample exportation, any global market regional clinical trial with a Chinese study arm should pursue local bioanalysis.

To improve engagement with the Chinese market, the NMPA has issued an array of guidance for bioanalysis over the past decade bringing regulations in line with international standards. In December 2011, it issued a guidance for clinical trial bioanalytical laboratory management, very similar to Good Clinical Laboratory Practice(s) (GCLP) elsewhere.

In 2015, the China Pharmacopeia issue a guidance for bioanalytical method validation, which is similar to U.S. and European Medicines Agency (EMA) guidances for bioanalytical method validation. Importantly, and also in 2015, the NMPA clarified the major considerations for on-site clinical data verification.

Currently, no formal guidance for immunogenicity exists in China, so they defer to U.S. and EMA standards. China representatives joined an expert working group for draft ICH M10 Bioanalytical Method Validation Guideline discussion and, once ICH M10 is implemented, China will follow the ICH guideline.

These changes in the Chinese regulation of bioanalysis have had major impacts. Since July 2015, NMPA has mandated self-inspection and verification of clinical data for NDA submissions, and clinical trial on-site inspections are now a routine step for NDA applications in China. In July 2017, NMPA issued a summary report on clinical data on-site inspections in the preceding two years focusing on data integrity and its critical importance for product launch in the region. This resulted in local, high-variability bioanalysis across multiple labs being rectified through mandated high-quality standards and routine inspection to confirm compliance.

Since then, both global and local biotech companies have implemented more stringent requirements for selection of bioanalysis contract research organizations (CROs), driving improvement across the industry. As a result, local bioanalysis quality now meets international standards, and Chinese hospital research institutes are regularly passing regulatory inspections from the U.S. FDA, Organisation for Economic Co-operation and Development (OECD), and NMPA.

ADDRESSING CHINA-SPECIFIC CHALLENGES IN SUPPORTING CLINICAL BIOANALYSIS

Clinical bioanalysis within China is made more difficult by an array of unique challenges with regard to regulation, supply chains, quality and expertise. These challenges include special NMPA requirements for China submission studies, special customs requirements, differences from global quality standards, variable quality standards from bioanalysis vendors, competitive markets for experienced personnel, along with implementing technological platforms supporting new drug modalities (e.g., cell gene therapy).

REGULATORY

From the regulatory side, the NMPA has a range of special requirements, such as all reports being in Chinese and requiring 100% of all chromatograms for validation and sample analysis reports, among others. At Covance, our primary recommendation is that companies select a lab with extensive experience supporting bioanalytical studies in China, as they have a better understanding regarding these special requirements for NMPA submission. We would also recommend the best practice of transferring fully validated methods to your partner CRO. Similar to special regulatory requirements from the NMPA, customs also has special requirements that can constrain key biological samples and reagents. To address this, it is best to employ an experienced logistic team to support the project needs and help resolve complex logistical issues.

QUALITY

Another key for success when performing bioanalysis in China is ensuring quality. Some of this challenge arises due to differences in the global quality standards. Creating a global quality system which ensures consistency across all bioanalytical sites, harmonizes best practices and incorporates learnings from regulatory inspection experience globally is ideal. Quality standards and technical expertise also vary among bioanalytical suppliers, so selecting a CRO with strong track record for international regulatory inspection and technical expertise is optimal.

Openness to study sponsor auditing of technical and quality assurance capabilities should be considered a requirement, and any CRO participating in a global trial should have a global quality system that ensures comparability of protocols and data across sites.

As part of ensuring quality, a CRO must address another major challenge of bioanalysis in China, which is the training and retention of experienced staff. Because the Chinese pharmaceutical development market is growing quickly, ample competition exists for qualified employees. Working with a well-known and experienced CRO will protect against loss of key employees within their operation

EXPERTISE

Finally, if the clinical trial is for a new treatment modality – such as cell or gene therapies – there are technical challenges in finding CRO support. Experience with new technology platforms and the ability to leverage U.S.- and European- best practices for cell and gene therapies is important. With Chinese regulatory reform, we anticipate more innovative drugs to be in clinical development, and bioanalysis labs in China will be gaining significant experience with these new modalities.

LOOKING AHEAD

The regulatory reform of the past decade is reshaping China's pharmaceutical R&D ecosystem to be more in line with global standards, spurring an era of growth in the region. Since NMPA-mandated self-inspection and outside study verification requirements were implemented in July 2015, high quality standards and routine inspection are expected in China, driving improvements in the in-country quality of regulated bioanalysis. While there are several distinct challenges in supporting the clinical trial in China, all are addressable through strategic planning and selection of a high-quality bioanalysis CRO.

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