



Drug Development Models in China and the Impact on Multinational Pharmaceutical Companies

By Ling Su, Ph.D.

China represents a huge potential opportunity for the pharmaceutical industry in both commercial and research and development spaces. In a recent survey,¹ one of the key themes that emerged was that China's role in global research and development is changing, and that biopharma firms that develop products in China will be better poised to take full advantage of market opportunities. At

the same time, China's evolving regulatory system, processes, and practices present unique challenges to the industry. Companies must gain a better understanding of the current landscapes, upcoming changes and their impacts, and develop strategies that are effective for China. This article describes various drug development models and the emerging trend in China, and discusses the impact on multinational pharmaceutical companies.



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Regulatory Framework for Drug Registration

The "Provisions for Drug Registration"² promulgated by the State Food and Drug Administration (SFDA, predecessor of today's China Food and Drug Administration, CFDA) provides the regulatory framework for drug registration in China. This regulation defines six registration categories for chemical drugs and 15 registration categories for biologics, ranging from new chemical entity or biologics to generics. Drugs marketed in

other countries but not yet in China are considered new drugs (category III). On the other hand, the registration procedures are promulgated based on whether the product is manufactured locally in China or in other countries. Therefore, two basic regulatory processes for new drug registration follow: new drug application for locally manufactured drugs and import drug application.

In the scheme of local manufactured new drug application, the applicant first applies for the authorization to conduct clinical trials with locally manufactured clinical supplies. The clinical data package requirement depends on the registration category that the product belongs to. For example, for a new chemical entity, a complete clinical program of phases I, II, and III trials will be required; for other new drugs, a pharmacokinetic study with a limited, local phase III, randomized, controlled trial will generally suffice. Upon the completion of the clinical program, an application is made for marketing authorization. New drugs approved under this scheme are entitled to a “monitoring period” of up to five years from the date of marketing approval. During this period, the agency will not approve any manufacturing or import application of the same drug or other formulations of the drug.

In the scheme of import drug application, the process of marketing authorization application can only start following approvals in other major countries (reference country) or the source country. The Certificate of Pharmaceutical Product (CPP) is needed for filing. Local clinical data in Chinese subjects are required. The first step in the process is to obtain a clinical trial authorization (CTA) to conduct a registration study, which is typically in the size of 200 patients for chemical drugs and 600 patients in the case of biologics.

A pharmacokinetic study in Chinese subjects is often required as well. Once the registration study is completed, the applicant submits the clinical data package along with other dossier for marketing approval and the issuance of an Import Drug License (IDL).

The drug registration regulation also acknowledges that data generated from China in an international multi-center clinical trial (IMCT) may be accepted to support a new drug application.³ In this case, the IMCT must conform with relevant clinical trial regulations in China such as regulation of CTA review and approval as well as Good Clinical Practice. The applicant must submit the complete study data package of the IMCT. However, since IMCT for biologics is currently not allowed in China, registration of biologics by foreign manufacturers will most likely follow the import drug application process by conducting a local registration trial.

In 2009, SFDA issued a “Special Review and Approval” regulation that provides fast track review and approval mechanism for certain drugs.⁴ Four categories of drugs are covered under this procedure: 1) those involving active plant, animal or mineral-based ingredients new to the Chinese market; 2) chemical drugs, active pharmaceutical ingredients, or biological products that have not been approved in China or a foreign country; 3) new treatment for AIDS, cancer, or other serious diseases; and 4) new drugs for diseases without effective treatments. Sponsors under these four eligible categories may apply to the agency for special approval procedures. Once granted, shorter review time may be expected. Applicants may also have access to the formal communication mechanism with, the reviewing body, to enhance information exchange and

discussion on important technical issues during review.

Over the past few years, the Center for Drug Evaluation (CDE) has implemented several measures in its internal review process in order to encourage applications of innovative products. CDE prioritizes reviews of clinical value-added innovative drugs, pediatric medications and drugs for rare diseases, as well as the projects under the “National Major New Drug Development Program”. It has also established a formal channel for CDE-sponsor meetings with signed meeting minutes available to the sponsor. Rolling submission is possible to reduce formal requests for supplemental data and to shorten review cycle time.

Models of Drug Development and Registration in China

For multinational pharmaceutical companies, the most straightforward approach to register a drug in China is to follow the import drug registration pathway as defined in the regulation (figure, a). The advantage of this approach is the high probability of success, because the drug has been approved in the source country or the reference country with the entire set of dossier available. The local registration study can be designed mimicking pivotal Phase III trials. The study has a limited scope and is limited in China only. Therefore, the investment required to manage and conduct the registration study is relatively small. However, the main disadvantage of this model is the drug lag from the time of first approval to the time of China approval. Since the CPP is required for filing the application, the earliest time point when the process can be started is at least 6 months following the approval in the source country or in a major country. The regulatory review time for CTA and NDA following the completion of the local

registration study may take up to 10 —18 months and 12 to 15 months, respective. Overall, the drug lag is typically five years or more. This is a significant barrier for Chinese patients to have access to innovative and potentially lifesaving therapies. In addition, because of the limited scope of local registration study, the China clinical data package is less comprehensive.

The second model that is much less utilized by multinational pharmaceutical companies as the initial introduction of a new drug into China is the local manufacturing model (figure, b). In this model, the drug is manufactured locally in China. Since the China approval is independent from the approvals in other countries, this model offers the potential for early launch of a drug in China. While the company can decide to start the process either before or after the drug is approved in other country, the earlier the development and application process starts, the higher likelihood there is to realize the maximum benefits. The “monitoring periods” extended to the new drugs approved in this model provides a de facto market exclusivity for up to five years. This model also provides the opportunity to generate a more extensive clinical data package including phases I, II, and III trials. The insight that the data offers and the experience gained with the drug in clinical trials could become a competitive advantage in the market place. However, the need for early planning and implementation of strategy as well as the investment required for local manufacturing should not be overlooked. The significant lead time and capital needed to establish the manufacturing facility and/or process could be substantial. The level of complexity to manage a local manufacturing project for a new drug product, especially in parallel of global development, could also be very high and challenging.

In the wake of the globalization of new drug development and the drug lag introduced by the traditional import drug registration model, alternative models have evolved over the years in order to accelerate new product registration in China. The ultimate objective is to bring new drug approval and launch timelines in proximity to the approvals in the USA, Europe, or Japan. These models can be described as simultaneous global development (SGD) – global trials (figure, c) or SGD – regional development (figure, d). In both scenarios, the company takes advantage of using IMCT for China registration.³

In the SGD – global trials model, China is included in the global clinical trial program. China may participate in one or more global phase III trials. Several conditions will need to be met for China registration: a sufficient number of patients from China (typically 100 patients per arm in the study and a local pharmacokinetic study) will need to be recruited; a separate China country study report with statistical evaluation is required. As the China development is part of the global program, there is no need to repeat or duplicate clinical studies in China. By shifting the start of China clinical trials to an earlier time point, China marketing application can be submitted along with the China clinical data soon after the global approval. The drug lag is hence possibly reduced to about 18 months or so.

The most significant hurdle for this model to be successful is two folds. Scientifically, potential regional differences in either intrinsic or extrinsic factors⁵ may limit China to become part of the global clinical study programs. Operationally, in light of the global project timeline, the long CTA approval time in China may reduce the chance for China to join the global clinical trials in time or leave

China only with a small time window for patient recruitment. Additionally, project management is more complex with China involved. Nevertheless, there have been numerous examples of successful implementation of this model, especially in the field of oncology and in programs involving large outcomes trials. Early strategy development and decision making is key to facilitate early CTA submission and to resolve any potential scientific and operational issues in the study design and execution.

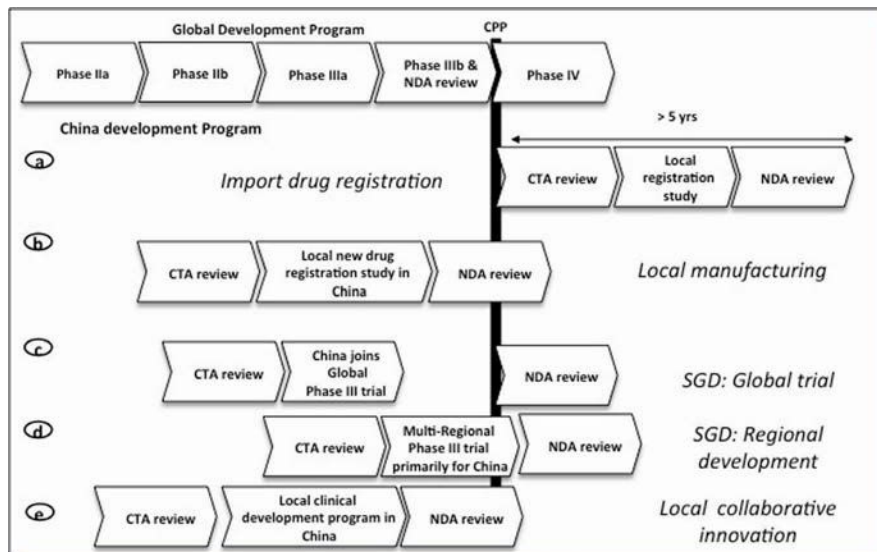
The SGD – regional development model shares a common feature as the SGD – global trial model, which is that the China development program is executed before the drug is approved in other countries. If managed well, early product approval in China can be achieved. The difference is, however, instead of China being part of the global program, a parallel development program is set up for China at the same time while the drug is being developed for the global market. There may be scientific rationales for taking this approach, such as ethnic sensitivity or medical practice issues that preclude China joining global trials. It is quite often based on operational or practical considerations. For example, the long CTA approval timeline in China may not allow the inclusion of China in global clinical development program, as mentioned above. It is also quite possible that the number of patients allocated to China in a global trial is not sufficient to meet the regulatory requirement for approval. Therefore, a separate China-centric development program is created. Strong drug development expertise and understanding of the epidemiology of disease and medical practice in China is critical to ensure successful implementation of such a China development program. While complex and of higher investment, the

China development program focuses on the specific medical situation and needs in China and the data is hence most applicable to the Chinese patient population.

An Emerging Model and the Opportunities and Challenges

Recently, partnerships between major multinational pharmaceutical companies and Chinese domestic companies or research institutes to collaborate on development of innovative medicines in China have become a notable trend. Several scenarios have emerged. The first is the licensing scenario. The second is a co-development scenario. The third scenario is even more dramatic: a joint venture is set up to develop a novel medicine in China.

Figure. Regulatory Pathways for Drug Registration in China



CPP: Certificate of Pharmaceutical Product; CTA: Clinical Trial Application; NDA: New Drug Application; SGD: Simultaneous Global Development

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This local collaborative innovation model (Figure, e) may be perceived similar to the “local manufacturing” model. However, it is important to realize that this model’s impact is much broader and significant. As it is treated as indigenous innovation by a local company, such program may qualify for various Chinese government policies encouraging innovation, including CDE’s development guidance and protocol assistance, possible “fast track” designation for faster regulatory review, and government R&D funding and other support in market access once the drug is approved. This model undoubtedly offers great potential for multinational companies to really “act locally” in conducting business in China. More importantly, the model offers the opportunity for the multinational pharmaceutical industry to develop and introduce innovative drugs to the Chinese market faster to meet the unmet medical needs.

The needs for strong drug development expertise and understanding of epidemiology and medical practice in China also apply in this model. The complexity

of identifying and working with the partner should not be underestimated. In addition, thorough considerations should be given to managing issues in intellectual property that may arise during the development process, legal, and other business aspects.

Conclusion

Under the current regulatory environment in China, each of the drug development models presents different advantages and challenges. Companies should evaluate and decide, early in the process of drug development, which model is most appropriate for their pipeline products for development in China. Such evaluation should be carried out in light of company’s portfolio, priority, competition, specifics of the product or program, and resources from both global and China point of view.

To make an informed decision and to successfully design and implement a China development program, possessing the “trust factor” with regulatory agency and the ability to gain regulatory insight, develop sound regulatory

strategies and to navigate the Chinese regulatory system, as well as strong local medical and drug development expertise are critically important success factors. ▲

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