Optimizing Drug Registration in China: Category I Route
EXECUTIVE SUMMARY

With a population of 1.3 billion and a pharmaceutical market growing at nearly 20 percent per year, China offers both huge opportunities and challenges for drug developers seeking to optimize development and product registration timelines. Multinational pharmaceutical companies are conducting more clinical trials in China as part of their international multicenter development programs. Chinese data from global multicenter studies now support the most common route to product registration in China—the category III route, an application for an import drug license.

However, the category III route to registration may not be the optimal pathway to the Chinese market for pharmaceutical products, in light of year-long review times required for clinical trial applications and the timing of subsequent marketing application submission and approval. The regulatory pathway for full category I new drug registration may offer advantages that compensate for the additional time and development work required. In this paper, PPD details advantages and disadvantages of the category I pathway.
INTRODUCTION

China is on track to become the world’s largest economy by 2050 and already boasts the world’s fastest growing pharmaceutical market. Now ranked third behind the United States and Japan, China’s pharmaceutical sales soared to $66.7 billion in 2011, propelled by a four-year annual growth rate of 23.5 percent. IMS Health projects that China will sustain a 15 percent to 18 percent growth rate over the next four years and replace Japan in the number two position, with sales exceeding $155 billion by 2016.¹

Access to China’s enormous market—and to its vast patient populations to support drug development—is fast-becoming an imperative for pharmaceutical research and financial success. In 2011, China sales of the top 10 multinational pharmaceutical companies were estimated at more than $20 billion.² However, China also poses enormous challenges for clinical development and product registration. Success in China depends especially upon navigating the country’s evolving regulatory landscape; developers must balance the great advantages of China’s large patient populations and efficient study enrollment with obstacles posed by registration pathways for new and existing drugs.

Introduction in China of drug products already approved in other markets represents a major opportunity for multinational pharma companies. Only 14 of the 140 new molecular entities approved in the world between 2006 and 2010 were available in China in 2011, compared to 39 in India and 91 in the U.S. Closing this gap means health gains for China as well as financial gains for multinational pharmaceutical companies.

The China Food and Drug Administration (CFDA), formerly the State Food and Drug Administration, considers drugs approved and marketed in other countries as new drugs in China. The CFDA designates previously approved therapies as category III “import drugs” and requires clinical data from trials conducted in China to support an application for an import drug license (IDL). This is the only option for drugs already marketed in another country. However, for drugs that have not been approved anywhere yet, developers might choose to conduct a full clinical development program in China and submit a category I new drug application to earn market approval that may be achieved several years earlier when compared to the category III route. In this paper, PPD compares these two strategies and discusses potential advantages of the category I approach.
CHINA’S REGULATORY LANDSCAPE: SIMILAR BUT DIFFERENT

In China, multinational companies operate in a climate of rapid change and increasing harmonization with research standards and processes of mature markets. They also encounter some dramatic differences compared to the regulatory processes of the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and other major drug regulatory authorities.

Similar Framework

China is working to improve and standardize drug research and regulation and has issued technical guidelines pertaining to chemical drugs, biologics as well as traditional Chinese medicines. The CFDA, which emerged in reorganization in 2003, establishes requirements for product registration, conducts oversight and monitors adverse events, enforces provisions for drug recalls and directs changes to drug import licensing.

CFDA regulation for new drug development is modeled on the U.S. FDA’s development pathway. To conduct clinical trials, CFDA requires a clinical trial application (CTA), similar to a U.S. FDA investigational new drug (IND) application. A three-phase clinical evaluation program is required to demonstrate drug safety and efficacy. Developers then submit a new drug application (NDA) for CFDA review, which includes review by the agency’s Center for Drug Evaluation (CDE) and National Institutes of Food and Drug Control (NIFDC).3

Key Differences: GCP Standards, Research Timelines and CMC Requirements

The CFDA has developed its own standards for Good Clinical Practices (GCP), Good Laboratory Practices (GLP) and Good Manufacturing Practices (GMP). The CFDA’s GCP standard has been evolving since its establishment in 1999; it was revised in 2003, and a guideline regarding ethics committee review was issued in 2010. Gaps remain between CFDA-GCP and ICH-GCP. Multinational drug developers must select study sites carefully and ensure that CFDA-GCP licensed investigators and research staff fully understand and comply with ICH-GCP as well.

A challenge for multinational pharmaceutical companies conducting trials in China results from differences in China’s review times, which are not aligned with those in other countries. Long review timelines for a CTA can erase timeline gains achieved by rapid patient enrollment. CFDA technical evaluation and administrative review takes from seven to twelve months, compared to 30 days for the FDA’s IND review and 60 days for an EMA CTA review.4 After a CTA is obtained, there is no clear regulation or guidance pertaining to amendments; when developers must amend a CTA, a new application must be submitted, whereupon the seven-to-twelve-month review must be repeated.

In addition, although China’s CDE recognizes the overall development process as established by the world’s major regulatory bodies and the different availabilities of data at various steps of development, CFDA currently has no clear, comprehensive guidance for technical (chemistry manufacturing and controls), preclinical or clinical requirements at the CTA stage. This essentially means that a comprehensive and complete set of technical, preclinical and clinical data is normally expected to support the CTA, a volume of data well above the typical requirements to support a U.S. IND or European CTA. China’s extended CTA process requires technical support to respond to queries and requests for additional data during the CDE review. Samples of the investigational drug, drug substance for biological products and reference standards must be made available for quality control testing by the NIFDC.

China’s clinical trial application has very comprehensive chemistry manufacturing and controls (CMC) require-
ments. For imported drugs seeking market registration, both sample testing and inspection of manufacturing sites are required at the time of CTA submission. Sample analysis and manufacturing must be conducted by Chinese facilities. Another challenge for multinational companies is China’s requirement for highly detailed manufacturing protocols—information that companies often consider proprietary. In compliance with the World Trade Organization (WTO) TRIPS agreement, China established a six-year data protection system for new chemical entities and a five-year “observation period” of product market exclusivity. However, multinational developers continue to be wary of possible threats to intellectual property rights.

TWO REGISTRATION PATHWAYS

Imported drugs account for the vast majority of drugs approved for marketing in China. To market imported drugs, a developer must apply either for a category III IDL (see table 1), or conduct a full development program in China (category I) and submit an NDA for new drug approval. In choosing between these two routes, developers need to consider the importance of CTA review time, since an approved CTA is required for both. Of key importance is also the expected timeline of approval of the drug in the rest of the world as, by definition, a category I drug must not have been approved in any other country at time of NDA application.

IDL Application
The IDL requires a clinical trial conducted in Chinese subjects for registration of new chemical entities and for all new clinical indications. A pharmacokinetic study is usually required, as well as a clinical study. The clinical trial application necessary to conduct studies can be submitted following approval of the new drug in the source country. Normally, it is required that 100 pairs of subjects (i.e. 100 treated patients) are recruited in China for a clinical trial under the category III IDL pathway, though this number can be subject to flexibility by the CFDA. The number of pairs is dependent upon protocol, indication and trial design and must deliver the appropriate level of statistical significance to the study.

The CFDA’s Provisions for Drug Registration permit the use of Chinese data from an international multicenter trial in the application for the IDL. More multinational developers are including Chinese trials in their global programs to gain access to large patient populations and collect data to support simultaneous registration in multiple countries, including China, using this IDL registration pathway. This pathway, however, may not be the fastest way to enter the Chinese market. On average, developers conducting global multicenter development programs experience a four-to-six-year lag between the product’s introduction in the U.S. and Europe and its introduction in China. This lag is due to the major differences in approval timelines, particularly for CTA reviews.

There are other regulatory barriers and trends in CFDA review that dictate caution in using the IDL pathway. Protocol variations and amendments are not supported under China’s current regulatory framework with requirements and timelines similar to those in other countries.

<table>
<thead>
<tr>
<th>TABLE 1. SIX CFDA CATEGORIES FOR CHEMICAL DRUG REGISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Category I: New drugs not yet approved in any country</td>
</tr>
<tr>
<td>+ Category II: Drugs seeking approval for a new route of administration not approved in any country</td>
</tr>
<tr>
<td>+ Category III: Drugs approved in other countries but not in China</td>
</tr>
<tr>
<td>+ Category IV: Drugs made by changing the acidic or alkaline radicals or metallic elements of the salt of a drug approved in China without changing the original pharmacological effects</td>
</tr>
<tr>
<td>+ Category V: Changed dosage form of a drug approved in China without changing the route of administration</td>
</tr>
<tr>
<td>+ Category VI: Generic form of a drug with existing national standards in China</td>
</tr>
</tbody>
</table>
Category I New Drug Application

Given the limitations of the category III IDL route, some developers are exploring the alternative—pursuing a category I NDA based on a full development program in China. The category I NDA is the default registration pathway for domestically-developed new drugs. The number of category I NDA approvals is increasing, according to CFDA reports on annual drug registration. New drug approvals rose to 10 in 2011, “marking a significant increase compared to 2009 and 2010.” According to a February 2013 CFDA report, the CDE completed first-time review for 47 CTA applications for category I and II (new route of administration) drugs in 2012. Final disposition of these applications made in 2012 has not yet been reported. The timelines for review look promising (see figure 1); more than 70% were reviewed in eight months or less.

A possible strategy for global development is to simultaneously conduct an international multicenter trial globally and a category I development program in China. This approach must be considered very early in program planning. If implemented successfully, the reward for developers can be earlier introduction in China, with new product entry into the Chinese market perhaps only a year behind the first global approvals, and potentially several years before the category III route (see figure 2).

To qualify as a domestic drug eligible for category I registration, developers must conduct appropriate toxicology studies and CMC development in China. This does mean that developers may have to repeat work that has been done elsewhere or commit to China as the global base for such development. Category I registration then

### TABLE 2. CATEGORY I REGISTRATION PROCESS

<table>
<thead>
<tr>
<th>Step</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>+ Manufacturing process transfer to Chinese company or facility</td>
<td>Developer licenses drug manufacturing process to local company for both active pharmaceutical ingredient (API) and finished product, or uses sponsor’s own China facilities.</td>
</tr>
<tr>
<td>+ CMC data generation</td>
<td>CMC studies conducted in API and drug product manufactured in China, including stability, specification and validation. Appropriate studies conducted to demonstrate comparability to same product produced outside China.</td>
</tr>
<tr>
<td>+ Preclinical studies</td>
<td>First-in-man studies can be conducted in China. Based on comparability study results, CFDA may accept preclinical pharmacology data from studies outside China. Safety studies must comply with GLP. GLP compliance statement and inspection of GLP records and results must be submitted to the CFDA.</td>
</tr>
<tr>
<td>+ CTA dossier preparation and submission</td>
<td>CTA must be approved to begin clinical studies. Phase I, II and III trials must be conducted in China for Chinese registration.</td>
</tr>
<tr>
<td>+ NDA/MAA submission</td>
<td>Chinese NDA applications must be submitted for CFDA review to earn market approval as a category I new drug.</td>
</tr>
</tbody>
</table>
requires Phase I, II and III clinical trials to demonstrate safety and efficacy for the China NDA submission and CFDA review. For products designated as domestic drugs, Phase I studies can be conducted in China (local first-in-man studies are not permitted under category III). The same disadvantages—long review timelines, unclear aspects of regulatory guidance and ensuring acceptance of Chinese data by the U.S. FDA, EMA and other regulators—pertain to the category I pathway; but for certain products and launch strategies, this route can offer important advantages.

The first three steps in category I registration—manufacturing process transfer, CMC data generation and preclinical studies (see table 2)—take a minimum of two years to complete. CTA approval takes approximately one year, and NDA approval takes approximately two years. The total timeframe is between four and five years. For registration via the IDL using Chinese data from global multicenter trials, the final approval date could be, at best case, around 18 months after a US or EU approval. For the category I route, this timing could be less than 12 months after US/ EU approval, or, in some cases, could result in the first global approval.

Exclusivity through Category I
There are additional benefits in terms of exclusivity. China’s State Intellectual Property Office (SIPO) grants patent exclusivity as supported by the TRIPS (Trade-Related Aspects of Intellectual Property Rights) agreement of the WTO. A patent application can be made at any time during drug development, and patents expire in 20 years from date of filing. Intellectual property also receives protection under provisions for an “observation period” of market exclusivity. Category I drugs are entitled to a five-year observation period, starting from the date of CFDA approval. Following approval, no new CTA applications for the same active moiety can be accepted for review; developers who have approved CTAs for the same active moiety, however, are permitted to continue clinical trials and submit NDAs to review. These provisions function independently; a product may be granted an observation period that runs concurrently with its patent but observation may not be added to extend patent life.

Approved category I drugs also receive six years of data protection. The CFDA will reject any application made by other applicants using undisclosed data of the approved drug without the original developer’s permiss-
sion, unless the follow-on applicant generated the data independently.

CONCLUSION

There are several appealing benefits to pursuing the category I new drug registration pathway, including:

+ Potential to launch in China within one year of U.S. or EU launch
+ Opportunity to market first in China without waiting for approval from another country
+ Cost-effective clinical studies and manufacturing
+ Ability to conduct first-in-human studies in China
+ Five-year observation period (market exclusivity) and six years of protection for clinical trial data, granted only to category I drugs
+ Opportunity to export product from China.

The most important benefit of category I registration is the time-to-market advantage. When developers conduct full, independent programs in China, they are not required to wait for approval in another country before applying for registration in China. This can potentially result in product launch in China several years earlier when compared to the category III IDL route.

REFERENCES


