NAVIGATING CHINA'S REGULATORY LANDSCAPE FOR COMMERCIAL SUCCESS

China has been identified by many multinational pharmaceutical companies as one of the most important strategic markets for future growth. However, the lengthy market access process could very likely undermine the growth opportunity. This article presents an overview of the regulatory framework governing pharmaceuticals, discusses regulatory development trends and analyses potential impacts on foreign pharmaceutical manufacturers.

The pharmaceutical industry in China is primarily regulated by the State Food and Drug Administration (SFDA), under the Ministry of Health (MOH), through the PRC Drug Administration Law, its Implementing Measures and a series of ministerial rules. SFDA is responsible for granting market authorizations for pharmaceuticals and their post-market surveillance. The agency is also responsible for defining and enforcing various good practices for preclinical studies, clinical studies, pharmaceutical manufacturing and distribution. MOH regulates healthcare providers and supervises the pharmaceutical procurement process at all public hospitals.

The State Administration of Industry and Commerce (SAIC) regulates pharmaceutical advertising and promotion. The State Administration of Quality Supervision Inspection and Quarantine (AQSIQ) regulates pharmaceutical importation. The National Development and Reform Commission (NDRC) regulates pharmaceutical pricing. The Ministry of Human Resources and Social Security (MOHRSS) regulates pharmaceutical reimbursement from the Chinese Basic Medical Insurance scheme.

Foreign pharmaceutical manufacturers must conduct a clinical study in China to obtain market authorization for their imported products. The manufacturer of an imported pharmaceutical product shall file for a Clinical Trial Authorization (CTA) with SFDA's Administrative Services Center, which will perform a formality review of the application dossier. Samples of the imported pharmaceutical product in question will be tested by the Drug Control Center at the port of entry to verify conformity with the quality standards. Once past the formality review, the submission will be handed over to the Center for Drug Evaluation (CDE) for technical review. CDE may also request supplemental information from the manufacturer. Upon completion of the technical review, the submission will be handed over to SFDA for an administrative review and issuance of the CTA. The statutory timeline for a CTA is 125 working days, but the actual timeline on average can take from 12 to 15 months.

Upon completion of the registration study, the manufacturer of an imported pharmaceutical product can file for market authorization, which is in essence an import approval and lasts for 5 years. SFDA normally only grants market authorization for an imported pharmaceutical product if it is already approved by the regulatory authority in the country where the manufacturer is located. The manufacturer shall submit the registration dossier with SFDA's Administrative Services Center for a formality review and samples of three batches of the product to be registered with National Institute of Control for Pharmaceuticals and Biological Products (NICPBP) to verify conformity with the quality standards. In the meantime, CDE will conduct a technical review of the clinical study data. Once reviewed, SFDA will perform an administrative review and issue the Import Drug License (IDL). The statutory timeline for an IDL is 185 days, but the actual timeline on average can take up to 18 months.

A fast-track review process may be available for newly discovered pharmaceuticals, pharmaceuticals containing novel active ingredients, pharmaceuticals treating AIDS, malignant tumours, rare diseases or pharmaceuticals with a superior clinical advantage. The procedure of the special review is similar to the normal regulatory review procedure, but the statutory timeline can be reduced by 40 days. Once receiving the market authorization, a pharmaceutical

manufacturer needs to address three main questions associated with market access: pricing, reimbursement and tendering.

Pricing, Reimbursement and Tendering

Drugs reimbursable from the Basic Medical Insurance, drugs with a PRC drug substance patent, anaesthetics, certain psychotropic drugs and blood products are typically subject to government-set maximum retail prices. NDRC is also entitled to set the ex-factory price or CIF price of birth control drugs and government-planned immunization drugs. The provincial government is entitled to set the maximum retail price of reimbursable OTC drugs on the National Reimbursable Drug List (NRDL) and drugs listed on the Provincial Reimbursable Drug List (PRDL).

The costs of pharmaceuticals can be reimbursed from the Basic Medical Insurance in China if these pharmaceuticals are listed in the NRDL or PRDL. The NRDL is issued by the MOHRSS and is divided into two classes. Class A of NRDL comprises those pharmaceuticals that are necessary and widely used in clinical treatment with good efficacy and lower prices in the specific category; they cannot be adjusted by any province. Pharmaceuticals on Class A of NRDL are fully reimbursable. Class B of NRDL comprises those pharmaceuticals that are available for clinical treatment with good efficacy and higher prices than Class A pharmaceuticals in the specific category. Provincial governments can vary up to 15% of drugs on Class B of NRDL to create a PRDL and decide on the actual reimbursement ratio for those drugs. Historically, the determination of reimbursability lacked a consistent process and allowed little transparency into the evaluation criteria. The thoughts of key opinion leaders in the relevant therapeutic areas of clinical practice played a dominant role. Health economics have not been systematically considered when setting drug prices or reimbursement status.

Drugs are procured by public hospitals through a collective bidding and procurement process in which manufacturers need to submit tenders in each province. The collective bidding and procurement system allows different bidding methods and may vary from one province to another, but drugs that are used widely or procured in large volume must be subject to competitive bidding. In addition to the bidding price, quality and innovation also play important roles when provincial health authorities decide on bid winners.

Noticeable Regulatory Developments

The Chinese government has implemented several initiatives that will impact the development of the regulatory environment.

National policies encourage industry consolidation and indigenous innovation: Several ministries published the 12th Five-Year Plans concerning the life sciences industry for the period of 2012–2017, in which innovation and industry consolidation are highlighted as national priorities. For example, the Ministry of Science and Technology sets the minimum pharmaceutical R&D targets at 30 new drugs and 30 new generic varieties by 2017. In the 12th Five-Year Plan concerning the pharmaceutical manufacturing sector issued by the Ministry of Industry and Information Technology, the agency aspires to foster five national leaders with annual sales of more than RMB 50 billion ($8 billion) by the end of 2017 and expects the aggregated market share of the top 100 domestic pharmaceutical manufacturers to exceed 50%. In the 12th Five-Year Plan concerning the pharmaceutical distribution sector issued by the Ministry of Commerce, the agency aims to foster 1–3 national leaders with annual sales exceeding RMB 100 billion ($16 billion) and around 20 regional leaders with annual sales exceeding RMB 10 billion ($1.6 billion). The aggregated market share of top 100 distributors is expected to exceed 85% and that of top 100 retailers is expected to exceed 60%.

SFDA continues to reform the regulatory framework and infrastructure: SFDA initiated an organizational reform at the CDE in 2011 aiming at reducing approval timelines. New drugs are eligible for parallel reviews at CDE for different parts of the application dossiers, whereas generic drugs are only eligible for sequential reviews. The queuing time for clinical trial approvals was reduced to 5.8 months from 9 to 10 months and that for new drug market authorizations is less than 8 months. In its regulatory reform plan issued in January 2013, SFDA emphasized the need to accelerate market access for innovative drugs. SFDA will reward drug R&D that delivers better therapeutic effects on critical diseases and leads to indigenous intellectual property by accelerated technical reviews and regulatory approvals for the resulting innovative drugs. SFDA will also explore the feasibility of performing technical reviews for innovative drugs along with the ethics review and consider allowing transfer of CTAs.

By contrast, SFDA intends to delegate certain approval authorities to provincial FDAs to ease workload at the national agency. A pilot program was implemented in Guangdong in 2012, under which the authorities of technical reviews and administrative reviews involving transfer of manufacturing technologies of pharmaceutical products were delegated by SFDA to Guangdong FDA. Guangdong FDA was also delegated to issue contract manufacturing permits for manufacturers based in Guangdong, with the exception of biologics and injectables made by traditional Chinese medicines.

Last but not least, SFDA is in the process of updating several key legislations governing the pharmaceutical industry, most notably the PRC Drug Administration Law and the SFDA Drug Registration Rules. In addition, SFDA recently amended the Good Supply Practice (GSP) for pharmaceuticals. The amended GSP enhanced standards on quality management systems and infrastructure of drug distributors and tightened control o the commercial and logistical flows of products. Drug distributors will have a 3 year grace period to comply with the amended GSP. Failure to comply at the end of the grace period will result in suspension or revocation of the pharmaceutical distribution permits.

The government is keen to ensure safety and quality of drugs: In the 12th Five-Year Plan for Drug Safety, the State Council requires strict compliance with Chinese GMP and GSP for pharmaceuticals and introduced a rating system for business integrity of pharmaceutical manufacturers, distributors and healthcare service providers. A national information disclosure system was launched on SFDA's website to blacklist companies or individuals directly responsible for serious violations of pharmaceutical laws or regulations for a debarment period of at least 2 years.

SFDA continues to roll out electronic barcoding to effectively prevent counterfeit drugs from entering into the legitimate supply chain as well as to efficiently recall pharmaceutical products with quality defects. Manufacturers of both domestically produced and imported narcotics, psychotropic drugs, blood products, vaccines, injectables made by traditional Chinese medicines, and drugs listed on the national or provincial Essential Drug Lists (EDL) must affix electronic barcodes to the external packages of the imported drugs. SFDA plans to subject all pharmaceutical formulations marketed in China to electronic barcoding by 2015 and will explore the feasibility of imposing electronic barcoding on active pharmaceutical ingredients. In addition, SFDA will include pharmaceutical retailers and healthcare service providers as covered stakeholders to further enhance traceability of drugs bearing electronic barcodes.

Another important initiative is the implementation of a quality consistency evaluation for generics. The first round of evaluation will focus on essential drugs and frequently used drugs during clinical practice. These generics will be compared with a reference product, typically the originator's drug, on predetermined pharmacological parameters to confirm quality consistency. Generic drugs that fail the evaluation will be withdrawn from the market.

Cost containment remains an important objective for healthcare reform: The overarching objective of the healthcare reform in China is to guarantee broad coverage of healthcare services at manageable costs. Several cost containment measures have been piloted in different provinces to cap spending of the Basic Medical Insurance (BMI) Fund, such as BMI budget control, a headcount-based payment scheme and a disease-based payment scheme. Moreover, the Ministry of Health plans to further apply collective bidding and procurement of pharmaceuticals to all public hospitals in China and open up the possibility for price renegotiation. Currently, collective bidding and procurement of pharmaceuticals only applies to public hospitals above county level and the renegotiation of bid-winning prices between manufacturers and hospitals is strictly prohibited. It is anticipated that county level hospitals will also be subject to the collective bidding and procurement mechanism and manufacturers will be expected to enter into another round of price renegotiation after winning the bids to supply to public hospitals in a given province.

Potential Implications for Multinational Pharmaceutical Companies

To maintain competitiveness, multinational pharmaceutical companies are advised to develop an accurate and up-to-date understanding of the Chinese regulatory framework and an adaptive market access strategy. Some high-level issues that companies may need to consider include the following:

The appropriate degree of localization. With respect to R&D activities, companies need to decide if they would like to engage in innovation (new compounds or new indications) or improvement (new dosage forms or delivery methods). For products manufactured outside China, companies might consider localizing the manufacturing activities in China in full or in part. Benefits associated with localization, such as reduced approval timelines and preferential tendering status, will have to be weighed against potential risks, including IP theft or the unintended disclosure of technical know-how.

The compelling competitive advantages. The domestic pharmaceutical industry in China has been dominated by generic manufacturers that have not heavily invested in R&D or manufacturing excellence. Foreign players should leverage quality and innovation as competitive advantages to optimize their positions in China. For example, foreign companies as originators of a generic product can set reference standards for quality consistency evaluation for generics and be entitled to preferential pricing and tendering status.

The counter measures for cost containment. China is a heterogeneous market and one size does not fit all. Companies should identify local variances in the implementation of cost containment measures at each province and adapt their market access strategies accordingly. Companies may also need to look into commercial opportunities in the self-pay segment to offset impacts arising from various cost containment measures.

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