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The Evolving Landscape of Drug Development in China

Innovation agenda includes expanded use of biosimulation

China's pharma market is poised for growth; it's expected to reach a value of approximately $120 billion by 2020. Today, China represents 20 percent of the world's population, which is estimated at 1.36 billion, but only 1.5 percent of the global drug market. From a demographic perspective, nine percent of the Chinese population today is over 65 years of age, and that number is expected to grow to 25 percent by 2050. Today, elderly patients make up 23 to 40 percent of the prescription drug market in China and 40-50 percent of the over-the-counter drug market. These trends represent a significant challenge for the Chinese and global pharmaceutical industry on many levels.

Generic drugs are the mainstay of China's pharma industry, representing 80 percent of all drugs sales in China in 2015. However, the overall percentage of generic drugs is declining as more novel drugs are introduced; generics comprised 92 percent of the Chinese market in 2007.

EXPEDITING NEW DRUG DEVELOPMENT

Pharma research and development (R&D) is at a relatively early stage in China. There is significantly less financing, fewer assets, and a smaller number of high-quality drug candidates to support this market segment than in the U.S., Western Europe, or Japan. Most important, the expertise and experience in both drug development and ability to navigate the regulatory landscape are just emerging as necessary competencies in China.

Another oft-cited obstacle to pharma innovation is the slow pace of the regulatory review process in China. During the past several years, the China Food and Drug Administration (CFDA) amassed a huge backlog of drug applications. While the average review time was three years, some companies waited as long as eight years for their drug to be evaluated. That delay was due in part to staff shortages, but also to the large numbers of applications being submitted for generic drugs of inferior quality.

The CFDA is working hard to expedite its drug approval process. The CFDA reported that it reviewed 9,394 new drug applications in 2015, which was a 90 percent increase over 2014. In 2015, the CFDA approved 241 registration applications for marketing chemical drugs, 76 for traditional Chinese medicines and natural medicines, and 25 for biological products.

STREAMLINING THE APPROVALS PROCESS

China's State Council released new policies designed to accelerate the approval process for innovative drugs in the second half of 2015. The "Opinions on Reforming the Review and Approval

Process for Drugs and Medical Devices," also known as the 'Opinions,' will have an impact on both Chinese and Western pharma companies.

For example, pharma companies will soon be permitted to conduct trials in China and other countries simultaneously. Furthermore, any clinical data obtained from international multicenter clinical trials involving a Chinese institution will be accepted as part of the application dossier in China.

Through the Opinions, the CFDA has undertaken to process all current drug applications by the end of 2016, and review them according to statutory timelines by early 2018.

The CFDA unveiled additional policies intended to improve the drug approval system in November 2015, and the major changes are as follows:

Starting on December 1, 2015, the CFDA began a three-year pilot program. Under this program, the domestic drug industry can obtain regulatory approvals to commercialize pharmaceuticals in principle and completely outsource the actual manufacturing to a contract manufacturing organization.

In addition, the fast-track approval pathway has been expanded. On February 26, 2016, the CFDA announced that it would give priority review to therapies for treating AIDS, tuberculosis, viral hepatitis, rare diseases, and cancer, and to medications developed for pediatric or elderly patients.

The classification of new drugs has also been revised. The term 'new drugs' now refers to pharmaceutical products that have never been marketed anywhere in the world or that represent improved forms of new drugs.

Furthermore, the approval process for clinical trials has been simplified. The CFDA will adopt a one-time umbrella approval procedure—rather than a phase-by-phase approval—for new drug clinical trial applications.

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IMPROVING DRUG QUALITY

The CFDA is also taking steps to improve the quality of data in new drug applications. On February 23, 2016, the agency published draft guidelines for its on-site verification of drug clinical trial data and then opened them up for public comments until March 3, 2016.

According to this draft guidance, pharma companies will be notified 10 days in advance of an impending visit by the CFDA's Center for Food and Drug Verification (CFDI). At that time, the company can decide whether to continue pursuing its drug registration application. After that 10-day period has elapsed, the verification process will proceed without delay. The local FDA will also be informed of this visit. After the verification process is complete, the CFDI will communicate its conclusion to the applicant and principal investigators within 10 days. False or incomplete clinical data may result in the CFDA's rejection of the relevant applications.

The CFDA is also endeavoring to improve the quality of its on-market drugs. During a State Council Information Office briefing on March 2, 2016, it was confirmed that the CFDA is asking pharma companies to carry out conformance assessments, testing the quality and efficacy of their approved generic drugs against the original formulation. This was not a mandatory requirement in the past. Pharma companies will now need to obtain the reference products and conduct the requisite research and clinical trials. The government will then evaluate the results. For generic drugs approved before Oct. 1, 2007, the conformance assessment of the oral solid dosage form needs to be completed by the end of 2018. Those drugs that were approved more recently have three years to pass the quality consistency evaluation. Any drugs that would not pass this test would have their approval number revoked.

INCREASING STAFFING LEVELS

In other efforts to expedite the regulatory approval process, the CFDA is opening a second drug evaluation center in Shanghai to support its main office in Beijing.

The CFDA is also increasing its staffing levels. Shanghai is the financial center and largest city in China. It offers a highly-skilled local workforce and a transportation hub with strong rail and air connections. Currently, there are only 120 employees in the CFDA responsible for technical review, even though the agency receives approximately 8,000 to 10,000 applications each year. That is far fewer staff than the U.S. FDA.

The shortage of drug development expertise in China is also curtailing innovation. China needs more experienced R&D professionals that understand the drug development process, have a global view, and can talk the same language as its Western partners.

Face-to-face meetings play an integral role in building long-term relationships in China. Most important decisions are made in person rather than by phone.

GROWING FOCUS ON INNOVATION

China's increased focus on innovation is already having a demonstrable impact on the industry. For example, hundreds of

pharma companies are now developing "me-better" and "bio-better" drugs. The CFDA is also working hard to expand their R&D capabilities. In the next five to 10 years, China is expected to develop several first-in-class or best-in-class pharmaceutical products.

Returning to the topic of China's priority review program, the inclusion of new technology as well as a focus on specific diseases, including oncology, rare diseases, and AIDs, point to a new generation of drug development optimization approaches. A similar program in the U.S. has resulted in profound improvements in novel drug approvals. In 2015 alone, 60 percent of the 45 newly-approved drugs by the U.S. Food and Drug Administration (FDA) were approved under one of the agency's expedited development programs. Additionally, 47 percent of those drugs were categorized as rare disease and 31 percent as oncology therapies.

With the Chinese Government's growing interest in developing novel pharma products, we are seeing increased adoption of modeling and simulation—also known as biosimulation—technologies. Physiologically-based pharmacokinetic (PBPK) modeling and simulation are used to determine first-in-human drug doses, predict drug-drug interactions, and understand drug disposition in untestable populations such as pediatric patients, pregnant women, and patients with co-morbidities or impaired organ function. It can also be employed to help select dose regimen, assess food effect on orally-administered medicines, and evaluate the impact of disease and lifestyle factors on drug disposition. Likewise, pharmacokinetic and pharmacodynamic (PK/PD) modeling and simulation are leveraged to make data-driven decisions at all stages of drug development through a quantitative framework, including dose selection, clinical trial design, competitive analysis, and a range of safety and efficacy factors.

Of the 45 drugs approved by the U.S. FDA in 2015, more than 90 percent leveraged biosimulation to inform that drug label. As a result, biosimulation will not only help bring safer therapies to market faster but also support China's fast-track drug approval process.

INCREASING USE OF MODELING AND SIMULATION

In the past, as the majority of drugs being produced in China were generics, pharma companies needed only to show that their product was an accurate reproduction of the brand drug. As a result, they tended to conduct only bioequivalence and non-compartmental analyses (NCA). The CFDA employs Phoenix software to conduct those types of analyses. The Phoenix platform is used to manage, analyze and report PK, PD, and toxicokinetic (TK) data.

But recently, as more Chinese pharma companies are beginning to develop new, innovative products, they have started to use pharmacometrics to conduct preclinical research. Furthermore, they are now conducting TK, PK/PD, and physiologically-based PK (PBPK) modeling, bringing pharmacometrics and biosimulation into clinical trials. Several top academic institutions, such as Peking University, Peking Union Medical College Hospital, China Pharmaceutical University, Huashan Hospital, and Fudan University are providing valuable industry support in this regard.

Peking University was recently named a Phoenix Center of Excellence. This Center of Excellence Program is designed to enhance research and training in pharmacometrics at elite academic centers around the world. Phoenix software and licenses have been donated to Peking University for teaching and research purposes. The institution is also receiving associated training and workshop assistance. The program goal is to combine Peking University's research, clinical, and educational expertise with Phoenix IT infrastructure to create new and innovative approaches to improving population health.

This TK and PK/PD analysis approach is now being used by pharma companies, clinical research organizations, academic centers, and hospitals. Pharmacometrics organizations and associations are also being founded in Beijing and Shanghai to help educate local scientists about this field, which they recognize is growing rapidly in importance. Attendance in pharmacometrics training courses is also increasing each year.

We are just starting to see the profound impact that biosimulation, model-based meta-analysis, and comparative effectiveness analysis can have on a drug candidate's development, regulatory review, and clinical application.

FUTURE OUTLOOK

Pharma innovation will continue to increase in China as product differentiation grows in importance. As a result, the percent of generics on the Chinese market will continue to decrease and the number of novel new drug applications will increase.

Biologics, especially biosimilars and bio-betters, will flourish in China. Many companies are already establishing good manufacturing practices (GMP), manufacturing capabilities, and developing biosimilars that target current blockbusters, such as Humira, Rituxin, and Herceptin. There are usually five to 15 competitors applying for regulatory approval for each target with the goal of selling these Chinese biosimilars in other regulated markets.

China's new policies show that it intends to be an active participant in the global drug development market and in commercializing new products. There are unprecedented opportunities in the Chinese drug development market today. **CP**

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