China

WILMERHALE

China Reforms Drug Registration

On July 10, 2007, China's State Food and Drug Administration (SFDA) promulgated the amended Measures on the Administration of Drug Registration (the Amended Measures), which will take effect beginning on October 1, 2007, superseding the original Measures, which were issued only two years ago. The Amended Measures were promulgated after two drafts, issued on March 10 and May 27, were published for comment by drug manufacturers, distributors, R&D institutions and the general public. The release of the Amended Measures came just one day after former SFDA Commissioner Zheng Xiaoyu was executed for bribery and dereliction of duty in allowing substandard medicines onto the market. The short period of time between the promulgation of the old Measures and the Amended Measures, coupled with the broad investigation into SFDA practices that has already resulted in the execution of the highest ranking government official to be sentenced to death since 2000, signifies recognition by the Chinese government of the urgent need to reform its ailing drug regulation system while also promoting innovation in the pharmaceutical industry.

The Amended Measures are intended to increase drug safety by enhancing quality and supervision requirements, as reflected in the following changes:

Narrowing the Scope of New Drugs

One of China's major regulatory shortcomings has been the fact that, until now, minor changes in drug formulations—differing from the original only in terms of preparation, method of administration or indications for which the drug may be prescribed—were registered as "new drugs." This policy resulted in the registration of more than 10,000 formulations a year as "new drugs," even though Chinese manufacturers typically invest no more than one or two percent of their revenue in R&D. "New drug" registration was pursued to obtain or extend eligibility for higher prices under China's government-controlled health insurance system.

Consistent with the original Measures, "new drugs" under Article 12 par. 1 of the Amended Measures are still defined as drugs that have not been marketed in China, rather than as novel chemicals or biological-based medicines. However, unless the new formulation purports to improve the quality and safety of the original drug and the new formulation's efficacy is manifestly superior to that of the original drug, any change in the preparation or method of administration, or any increase in the indications for which a drug may be marketed in China, will no longer be grounds for registration of the product as a "new drug"; instead, it will be filed with SFDA under the existing drug registration, pursuant to the same procedure for registration of new drugs under Article 47.

Creating a Regulatory Procedure for Generic Drugs

The term "follow-on drug"—defined under the original Measures as a "drug subject to existing national standards" (已有国家标准的药品)—has been renamed "generic drug" (仿制药) under Article 12 par. 3 of the Amended Measures. Under Article 74, a generic drug is defined as having the same active pharmaceutical ingredient (API), method of administration, dosage form, specification and efficacy as the original drug. An applicant for manufacture of a generic drug is required to submit comparison data/materials between the generic drug and original drug. Significantly, under Article 12 par. 3, biological drugs must comply with the new drug registration procedures rather than the generic drug registration procedures.

Transparency

The Amended Measures require that SFDA and local food and drug administration bureaus provide drug applicants with comprehensive information on the application process—including application procedures, application charges, timelines, required application materials and lists of officials in charge of the application and inspections—which, under Article 8 par. 2, must be publicly posted on

the SFDA website and on the websites or premises of the local bureaus. To prevent corruption, Article 6 provides that officials with a possible interest in the applicant or application shall not be involved in the approval process. In addition, with respect to licensing issues that directly involve significant interests among the applicant and other relevant interested parties, new provisions involving procedures for public hearings (听证) are detailed under Article 7. In such cases involving multiple interested parties, SFDA or the local bureau will—prior to the grant of the administrative license (e.g., approval of a new drug registration)—inform the applicant and relevant interested parties of their rights with respect to requests for public hearings, representation and defense.

Approval Authority

To reduce corruption and strengthen oversight over the drug approval process, Article 6 provides for the establishment of a collective decision-making system for drug administration officials who participate in the approval process, rather than placing ultimate authority with one person. In addition, while retaining its approval authority over major matters, SFDA, under Articles 114, 115 and 124, will delegate part of its drug registration approval authority to provincial-level bureaus (e.g., with respect to re-registration and supplementary registration). This is a shift from the practice introduced by the late Commissioner Zheng, who centralized all such approval authority in SFDA in 2003.

Verification of Application Materials

Article 13 of the Amended Measures requires that the applicant provide sufficient and reliable research data to ensure the safety, efficacy and quality of the drug, and shall be responsible for the authenticity of the application materials. It requires that the drug administration authority conduct on-site inspections of non-clinical trials, clinical trials and manufacturing facilities to ascertain the authenticity, accuracy and completeness of the application materials before a drug can be approved for marketing. In addition, Article 49 stresses that the applicant may not supplement technical data on its own during the drug registration application process, except for applications subject to the special approval procedure (see below) or new findings relating to efficacy. SFDA, under Article 166, will not accept or approve an application for clinical trials that includes false samples or data, and—under such circumstances—will bar reapplications for a period of one year and may also move to revoke prior clinical trial approvals and bar reapplications for a period of three years. Under Article 167, SFDA will not accept or approve an application for drug manufacture that includes false samples or data and will bar reapplication for a period of one year, and may also revoke prior approvals and bar reapplications for a period of five years.

Special Approval

Under Article 45 of the Amended Measures, traditional Chinese medicines (TCM) not previously marketed in China; APIs, along with their preparations and biologicals not marketed in China or elsewhere; new drugs with superior efficacy for AIDS, malignant tumors or orphan diseases; and new drugs for diseases for which there is not yet an effective therapy may be entitled to a "special approval procedure," which was previously referred to as an "express approval procedure" under the original Measures. Qualifying drugs may request the special approval procedure during the drug registration application process, subject to the discretion of SFDA's Drug Review and Evaluation Center (药品审评中心).

Speedier Approval Timeline

Article 150 of the Amended Measures sets forth clear and speedier timelines for reviewing new drug applications: (1) 90 days for new drug clinical trial applications and 80 days for those entitled to special approval; (2) 150 days for new drug manufacture (新药生产) applications and 120 days for those entitled to special approval; (3) 160 days for applications for drugs already marketed, but with a changed dosage form or generic drugs; and (4) 40 days for supplementary applications requiring technical review. After the technical review has been completed, SFDA is to determine whether to approve an application within 20 days. Imported drugs are to be reviewed under timelines taking the above as reference points. In other words, imported drugs may be subject to longer review periods.

Monitoring Period

With respect to new drugs subject to Monitoring Period protection that have not been manufactured within two years after the grant of the Monitoring Period, SFDA, under Article 69, may approve an application for the same new drug by another manufacturer who will be subject to protection for a de novo Monitoring Period (rather than the remainder of the existing Monitoring Period).

Clinical Trials

The Amended Measures do not provide any significant changes with respect to clinical trials. In particular, under Appendix III—which applies to the registration of biological drugs—no changes have been made to the classification of biological drugs or the requirements for clinical trials and application documentation, which means that all biological drugs will still be subject to full-phase clinical trials.

Conclusion

The Amended Measures promise to improve registration procedures by upgrading drug appraisal and approval standards to enhance the focus on drug safety while encouraging innovation. The Amended Measures also call for tighter supervision during the application process, both for products and on-site production. Some more routine procedures are delegated to provincial bureaus, which will free the SFDA from some burdens. To reduce corruption, the Amended Measures stress that drug registration must comply with the principles of "opening, fairness and justice," and that drug approvals must be based on collective—rather than one-person—decisions, with the official in charge of the approval procedure responsible for the conduct of the procedure.

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