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China's New Drug GMP: Higher Standards, New Compliance Philosophy

By Lei Li

On February 12, 2001, China's Ministry of Health published the final version of China's long-awaited new drug good manufacturing practices regulations (GMP 2010), which became effective on March 1, 2011.¹ Subsequently, China's State Food and Drug Administration (SFDA) published the staggered implementation plan for GMP 2010² and promulgated several key regulations for the implementation of GMP 2010. SFDA also announced its commitment to the active enforcement of GMP 2010.

Compared with its several previous versions, GMP 2010 significantly heightened the drug manufacturing quality requirements in China. Most of its key provisions are aligned with the GMP provisions in the United States, and EU (but modeled more on the EU system). However, GMP 2010 has certain unique provisions as well. Multinational companies producing drugs in China need to review their manufacturing systems comprehensively to ensure full compliance with GMP 2010 but should not rely on compliance with U.S. or EU GMP regulations.

Overview of GMP 2010

Drug GMP regulations have a much shorter history in China than in the U.S. and the EU. The concept of drug GMP was introduced into China in the mid-1980's, and it was not until 1985 that SFDA published the draft of China's first drug GMP. SFDA promulgated China's first drug GMP in 1988 and subsequently revised it in 1992 and 1999.

The previous version of the drug GMP, with only 88 articles, was a simple compilation of basic quality control requirements for drug manufacturing. In comparison, GMP 2010 has 14 chapters and 313 articles and contains much more detailed requirements on key aspects of the manufacturing process for drugs.

In GMP 2010, SFDA has adopted a new philosophy on GMP compliance, which shifts the focus of SFDA's GMP review from requiring the drug manufacturer to meet certain stipulated technical standards to requiring them to maintain and operate a comprehensive and effective drug quality control system. Guided by this new philosophy, SFDA has revised most of the key requirements in the drug GMP. For example, the personnel

requirements have shifted from the qualifications of the personnel to their responsibilities and the necessary experience and expertise for the performance of those responsibilities. Similarly, the focus of the sampling and testing requirements was shifted from the enumeration of the items to be tested to the testing procedures and methods themselves.

SFDA's new philosophy is embodied in the following key changes in GMP 2010:

- Introduction of the concept of "Quality Risk Management" system, which covers many key aspects of drug manufacturing quality control, such as supplier audits, change control, corrective, and preventive actions (CAPA) and Product Quality Review;
- More specific requirements on the development and update of standard operating procedures (SOP);
- Detailed requirements on the making and retention of batch records;
- Key technical requirements in the drug manufacturing process. In particular, GMP 2010 adopts the EU clean area classification system in the manufacture of sterile products;
- Responsibilities of "Key Personnel" in the manufacturing process and quality control of drugs, including the Company Head, Manufacturing Management Responsible Person, Quality Management Responsible Person, and Qualified Person. SFDA has acknowledged that the responsibilities of the Quality Management Responsible Person and Qualified Person may overlap, and will elaborate on the division of their responsibilities in its agency rules.

Generally, GMP 2010 was modeled on EU's GMP regulations,³ relevant guidelines of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and the World Health Organization (WHO) Guide to Good Manufacturing Practice (GMP) Requirements. GMP 2010 also drew on certain provisions in the U.S. GMP regulations.⁴ Therefore, the overall structure of GMP 2010 and its main provisions are compatible with but not the same as those in the above regulations.

On February 24, 2011, SFDA issued GMP implementation guidelines in the form of appendices to GMP 2010 for five categories of products: sterile drugs, active pharmaceutical ingredients (APIs), biological products, blood products, and Traditional Chinese Medicine (TCM) preparations.⁵ The implementation guidelines set forth further detailed GMP compliance requirements for these product categories. The agency is expected to publish guidelines for other categories in the future.

Despite the heightened requirements in the regulations, GMP 2010 has some potential regulatory gaps as well. First, manufacturing of APIs solely for export purposes is exempted from the GMP requirements in China, unless the manufacturers are registered as drug manufacturers at SFDA. This situation previously resulted in incidents involving China's exported APIs. To the dismay of many stakeholders, particularly U.S. and European drug manufacturers using APIs from China, GMP 2010 and its implementation regulations did not make any direct efforts to remedy this regulatory loophole, although an indirect supplier qualification door has been opened. Second, although SFDA published a GMP regulation for drug excipients in March 2006, GMP certification for drug excipients has never been made mandatory. GMP 2010 did not alter this.

GMP Certification Procedures

On August 2, 2011, SFDA issued the final Rules for Drug GMP Certification (the Certification Rules).⁶ The Certification Rules provide that SFDA is responsible for GMP certification and follow-up inspections for injections, radiological and biological drugs, and GMP inspection of imported drugs. Provincial FDAs are responsible for other drugs.

Drug manufacturers must submit their drug GMP certification applications to provincial FDAs. For drugs within the jurisdiction of SFDA, provincial FDAs will forward the applications to SFDA. SFDA or provincial FDAs will review the applications within 20 business days and then organize the on-site inspections within 40 business days.

The on-site inspection team will consist of at least 3 inspectors who are selected randomly from SFDA's GMP Inspector Database. The inspection team will give prior notice to the drug manufacturer about the on-site inspection, and the inspection will ordinarily last 3 to 5 days. After the inspection is completed, the inspection team will perform a risk evaluation of the drug manufacturer.

The drug manufacturer must take corrective actions for defects that are discovered by the inspection team and report such corrective measures to the SFDA or provincial FDAs. The drug manufacturers may raise objections to the inspection team if they do not agree with the discovered defects.

The inspection team will, on the basis of the inspection findings, make a recommendation to the SFDA or provincial FDAs. Within 40 days after receiving the recommendations, the SFDA or provincial FDA will evaluate the effectiveness of the corrective measures taken by the drug manufacturer and make a final determination on whether to grant GMP certification to the drug manufacturer.

Evaluation Criteria in GMP Certification

The Certification Rules divide all GMP compliance defects found in the course of GMP on-site inspections into the following three categories:

- Serious Defects, *i.e.*, serious deviations to drug GMP requirements that may result in products causing injuries to users;
- Major Defects, *i.e.*, significant deviations to drug GMP requirements; and
- General Defects, *i.e.*, deviations from drug GMP requirements that do not rise to the level of serious defects or major defects.

After receiving the on-site inspection team's reports on discovered defects, SFDA or provincial FDAs will make their determination following a Risk Evaluation Method:

The drug manufacturer will pass the GMP certification if the on-site inspection only discovers General Defects. Even if certain Major Defects are discovered, the correction of all Major Defects and General Defects proves that the drug manufacturer has the ability to take effective measures for correction; and

The drug manufacturer will be denied GMP certification if: 1) the inspection discovers any Serious Defects or multiple Major Defects that show the manufacturer has failed to take effective control of its manufacturing process; or 2) if the correction or the plan for correction of Major Defects and General Defects cannot prove that the drug manufacturer has the ability to take effective measures for correction.

The Certification Rules also provide that when making the determination, SFDA or provincial FDAs may combine a number of defects and elevate them to a higher level of defect if such determination is justified by the accumulation of these defects. A corrected defect may be downgraded to a lower level of defect. In addition, SFDA or provincial FDAs should conduct on-site inspection after the completion of the corrective measures for any Major Defects.

Under the previous version of drug GMPs, SFDA divided GMP compliance defects found in on-site inspections into two categories, *i.e.*, Serious Defects and General Defects, and made a GMP certification decision on the basis of the pass/fail

percentage of 259 inspectional items. The abandonment of this mechanical approach in GMP 2010 and its focus on the overall effectiveness of the manufacturer's quality management system are another proof of SFDA's new, realistic compliance philosophy in drug GMP regulations.

Implementation Schedule; Future Reform

GMP 2010 became effective on March 1, 2011 and SFDA will implement the new regulation in three stages.

From March 1, 2011, all newly incorporated drug manufacturers and newly established, rebuilt, or expanded drug manufacturing facilities must meet GMP 2010 standards. Foreign manufacturers must review this provision carefully.

Manufacturers of sterile drugs (including blood products, vaccines, injections, etc.) must meet GMP 2010 standards before December 31, 2013.

Manufacturers of all other drugs must meet GMP 2010 standards before December 31, 2015.

More importantly, however, SFDA currently requires GMP certification for each new dosage form or production line of a drug manufacturer. As early as 2008, SFDA indicated that it would work toward requiring GMP certification for each newly-launched drug product. The effectiveness of GMP 2010 has made this goal possible, and we expect that SFDA will take concrete measures to push forward this reform in the coming years.

SFDA issued several notices beginning in February 2011 requiring drug manufacturers to develop implementation plans, upgrade facilities, and improve overall quality management systems to ensure compliance with GMP 2010 before the stipulated timelines. The implementation of GMP 2010 and the ensuing surge of GMP inspections will pose significant challenges to the resources that SFDA may deploy, as well as the GMP proficiency and drug manufacturing knowledge of the GMP inspectors. Therefore, SFDA's current implementation efforts have focused on the training of GMP inspectors. On August 2, SFDA issued the final Rules for Retention and Evaluation of Drug GMP Inspectors, setting forth the qualification requirements for GMP inspectors. SFDA is expected to substantially increase GMP inspections and enforcement actions after the inspectors have been sufficiently trained.

Lastly, SFDA is also in the process of revising various implementation regulations for GMP 2010, hoping to standardize the GMP inspection procedures and give drug manufacturers more opportunities to interact with the FDA authorities in the GMP inspection process. Companies are advised to watch the developments in these areas closely.

Huge Impact on Market Landscape in China

In the past several years, the Chinese Government has been under tremendous pressure, both domestically and internationally, to impose higher standards on drug manufacturing activities to ensure the quality of drug products manufactured in China. The promulgation of GMP 2010 demonstrates the Chinese government's determination to upgrade China's drug manufacturing quality system and advance Chinese drug companies' competitiveness in the international market.

The implementation of GMP 2010 will very likely change the landscape of China's drug market. Currently, the manufacturing quality of domestic Chinese companies is comparatively low, and it is estimated that domestic companies need to make investments worth tens of billions of U.S. dollars to upgrade their manufacturing facilities and infrastructures to meet the requirements of GMP 2010. As a result, a huge number of small-sized drug manufacturers may be eliminated from the market, and the manufacturing costs and prices of the remaining drug manufacturers will increase significantly.

Multinational drug companies in China may find it less burdensome to meet the requirements in GMP 2010. Nevertheless, GMP 2010 contains numerous unique requirements that are different from the U.S. and ICH/EU GMPs, and multinational drug companies need to review their manufacturing practices in China comprehensively to ensure full compliance. Moreover, they also need to take new GMP standards into account in their mergers and acquisitions and joint venture projects in China to ensure that their acquisition targets or joint venture partners comply with GMP 2010. ▲

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1. Chinese version is available at: <http://www.sfda.gov.cn/WS01/CL0053/58500.html>.
2. SFDA Notice on Implementation of GMP 2010, Chinese version available at: <http://www.sfda.gov.cn/WS01/CL0844/59017.html>.
3. EU Good Manufacturing Practices: Medicinal Products for Human and Veterinary Use.
4. 21 CFR part 211.
5. Chinese version is available at: <http://www.sfda.gov.cn/WS01/CL0087/59026.html>.
6. Chinese version is available at: <http://www.sfda.gov.cn/WS01/CL0055/9974.html>.