

E-ALERT | Life Sciences

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SFDA SEEKS PUBLIC COMMENT ON PROPOSED DRUG GMP INSPECTION REGULATIONS¹

On April 25, 2011, the China State Food and Drug Administration (“SFDA”) issued a notice to the provincial or equivalent level food and drug administrations (“PFDA”), seeking PFDA and public comments on proposed regulations establishing procedures for pharmaceutical good manufacturing practices (“GMP”) inspections in China or abroad (“Proposed Regulations”).² Comments are due by May 15, 2011. When effective, the Proposed Regulations will supersede China’s current pharmaceutical GMP inspection regulations (“Current Regulations”), which have been in effect since October 1, 2005.

The Proposed Regulations impose many new requirements that will have substantial impact on both foreign and domestic pharmaceutical companies doing business in China. Most importantly, the Proposed Regulations set up a process by which the SFDA and PFDA can more easily refuse, suspend, or revoke a manufacturer’s GMP certification. The Proposed Regulations achieve this result through four separate mechanisms: (1) imposing a requirement for biennial inspections; (2) adopting a risk-based approach and adding one new defect classification; (3) expanding the circumstances under which the SFDA or a PFDA can take enforcement actions; and (4) establishing certain timelines for GMP certification review and action.³

New biennial inspection requirement

For each manufacturer that has been issued a GMP certificate, the Proposed Regulations require SFDA or the relevant PFDA to conduct at least one follow-up inspection every two years, during the 5-year GMP certificate period.⁴

¹ Nothing contained herein should be deemed to be a formal legal opinion with regard to People’s Republic of China (PRC) law or to provide assurances with regard to the success of any particular course of action to be taken. Only qualified nationals of the PRC working in PRC law firms are permitted to practice PRC law. Accordingly, as is true for all non-PRC law firms, we cannot express any legal opinion concerning the interpretation or application of PRC law.

² *SFDA Notice and Proposed Regulation*, available at <http://www.sfda.gov.cn/WS01/CL0778/60981.html>.

³ SFDA oversees GMP inspection and certification of injectable, radioactive, and biologic drugs, as well as international inspection and certification. PFDA oversees GMP inspection and certification of drugs other than injectable, radioactive, and biologic drugs, as well as any other inspections and certifications delegated by SFDA. See Articles 2 and 3, Proposed Regulations.

⁴ See Article 29, *Proposed Regulations*.

New risk-based approach for classification of defects

The Proposed Regulations require that the inspection division of the SFDA or a PFDA must evaluate defects found during an inspection based on the level of risk they present. This evaluation must take into account, among other things, the product type and the nature and frequency of the defect. The Proposed Regulations define defects in three classifications:

- **Serious defect:** a serious deviation from any drug GMP requirement that results in injury to a user or imposes any health risk;
- **Major defect:** a major deviation from any drug GMP requirement; and
- **Ordinary defect:** a deviation from any drug GMP requirement that is not a serious or a major defect.⁵

This risk-based approach and the hierarchy of defects are not found in the Current Regulations or the two classification system set up in the Criteria for Determination of Pharmaceutical GMP Inspection (“Inspection Criteria”). SFDA issued the Inspection Criteria in October 2007, and they have been effective since January 1, 2008.⁶ The Inspection Criteria serve as a checklist for inspectors during an inspection to evaluate compliance with GMP requirements set forth in the GMP regulations.⁷ The Inspection Criteria describe 259 GMP requirements, designating 92 as essential requirements, and 167 as ordinary requirements.⁸ Any failure to meet an essential requirement is deemed a serious defect, and any failure to meet an ordinary requirement is deemed an ordinary defect. The Inspection Criteria do not have the “major defect” classification, and they do not use a comprehensive risk-based approach. Any risk evaluation under the Inspection Criteria is reflected through the designation of a particular GMP requirement as an essential requirement, and failure to meet such an essential requirement as a serious defect.

The Proposed Regulations also require that SFDA and PFDAs classify the results of inspections as either “conformance” or “nonconformance.” This conformance or nonconformance classification must be based on the principle of risk evaluation, and consider the nature and seriousness of any defects, as well as the type of product.

⁵ See Article 24, *Proposed Regulations*.

⁶ *Inspection Criteria*, available at <http://www.sfda.gov.cn/WS01/CL0845/26010.html>.

⁷ China’s GMP rules are set forth in the *GMP Rules for Pharmaceutical Production*, which were recently revised and issued on February 12, 2011 by China’s Ministry of Health, available at <http://www.sfda.gov.cn/WS01/CL0053/58500.html>. (“2010 GMP Rules”)

⁸ The 259 requirements set up in the Inspection Criteria have been serving as a very useful inspection tool, when the previous GMP rules contain only less than 90 requirements. However, the 2010 GMP Rules now has set up more than 300 requirements that are applicable to all drugs, and many additional requirements that apply to biologics, sterile drugs, blood products, ingredients, or traditional Chinese medicine prepared in dosage forms. Accordingly, it is believed that the Inspection Criteria will be gradually phased out because its 259 requirements are not as comprehensive as those in the 2010 GMP Rules.

- *Conformance*. The inspection division can make this determination when: (1) there are only ordinary defects, or (2) the corrective actions or corrective action plan for all major and ordinary defects show that the manufacturer can implement necessary actions to correct the defects.⁹
- *Nonconformance*. The inspection division can make this determination when (1) there are one or more serious defects, or several major defects, showing that the manufacturer does not have effective control over the entire production; or (2) the corrective actions or corrective action plan for all major and ordinary defects do not show that the manufacturer can implement necessary actions to correct the defects. If the determination is nonconformance, the manufacturer has not passed the inspection, and must re-apply for GMP certificate.¹⁰

By comparison, under the Inspection Criteria, whether a manufacturer can pass an inspection and obtain the GMP certificate is determined somewhat numerically. The Inspection Criteria provide that no GMP certificate can be issued if there is one or more serious defect, or if there are more than 20% ordinary defects. Calculation of the 20% threshold is as follows: Failure to meet one requirement is counted as one defect; 20% means that there are 34 or more ordinary defects out of the possible total of 167 ordinary defects.¹¹ Conversely, a GMP certificate may be issued if (1) there is not a single serious defect; (2) ordinary defects are 20% or less (i.e., 33 or less ordinary defects out of the possible total of 167); and (3) the facility has corrected the defects or submitted corrective actions plan.¹²

In short, the criteria in the Proposed Regulations for determining defects and conformance or nonconformance intend to improve the decision making by requiring the risk-based evaluation, rather than numerical calculation, and allow for consideration for all the facts and circumstances. It is believed that the Proposed Regulations, when effective, will also supersede the Inspection Criteria.

Expanded provisions for suspension or revocation of GMP certification

The proposed regulations expand the circumstances under which SFDA or a PFDA may suspend a manufacturer's GMP certificate. These circumstances now include where:

- the facility fails to comply with GMP requirements;

⁹ See Article 25(a), *Proposed Regulations*.

¹⁰ See Article 25(b), *Proposed Regulations*.

¹¹ 167 is the number of total possible ordinary defects. The denominator for calculating the 20% threshold can be smaller because, for some types of drugs, the total number of possible ordinary defects is less than 167. See *Inspection Criteria*, available at <http://www.sfda.gov.cn/WS01/CL0845/26010.html>

¹² See Articles 1, 3, and 6, *Inspection Criteria*.

- the facility has been required by the government to suspend production; or
- *other circumstances exist that require a suspension.*¹³

The last item, “*other circumstances exist that require a suspension*” is the new provision. Its scope suggests that SFDA or PFDA can suspend a GMP certificate any time it believes that the situation warrants the suspension. After the suspension, the SFDA or the relevant PFDA can require the manufacturer to correct the problems. SFDA or the PFDA will then return the GMP certificate when the manufacturer has completed the corrections and passed the on-site inspection.¹⁴

The Proposed Regulations also expand the circumstances under which SFDA or the relevant PFDA may revoke a manufacturer’s GMP certificate. These circumstances include where:

- the manufacturer’s production permit has been revoked;¹⁵
- the manufacturer’s production scope has been reduced;¹⁶
- the manufacturer commits serious violation of any laws and regulations, or has many serious GMP defects and presents higher product quality risks; and
- other circumstances exist that require a revocation.¹⁷

Similarly to circumstances for suspension, the last item, “*other circumstances exist that require a revocation*” is the expanded item. It is unclear whether the circumstances for suspension or revocation must come from an initial, follow-up, or for-cause inspection. Presumably, the finding can come from any inspection or any source and at any time, because the Proposed Regulations do not specifically limit the finding of the circumstances to any type of inspections or sources from which the SFDA or PFDA learn the existence of the circumstances.

Specific timelines for application, inspection, response, and determination

Finally, the Proposed Regulations also impose more timelines for review, inspection and response. For example,

- Within five working days of receipt of an application for GMP certification, the SFDA or relevant PFDA must (a) complete the format review of the application

¹³ See Article 35, *Proposed Regulations*.

¹⁴ See Article 36, *Proposed Regulations*.

¹⁵ A manufacturer needs to apply for or renew a drug production permit before it can apply for GMP certification. PFDA handles the review, issuance, and renewal of production permits. The criteria for issuance include non-GMP related factors, such as whether production of the drugs will be in line with the national policy and planning of pharmaceutical industry.

¹⁶ A drug production permit will specify the types of drugs the manufacturer is permitted to produce.

¹⁷ See Article 37, *Proposed Regulations*.

and, (b) if the application is accepted for filing, pass the application to its inspection division for technical review.¹⁸

- Within 20 working days thereafter, the inspection division must complete its technical review of the application. If additional information is required, the inspection division must notify the applicant, and the 20 day clock resets. The applicant then has 60 days to submit the information required. Failure to do so terminates the application.¹⁹
- Within 40 working days after completion of its technical review, the inspection division must finalize the on-site inspection plan, notify the manufacturer, and conduct the on-site inspection.²⁰
- Within 20 working days after completion of an on-site inspection, the manufacturer must complete necessary corrections and submit the documentation of such corrections, or submit the corrective action plan, to the inspection division.²¹
- Through a series of internal deadlines, SFDA or the relevant PFDA then has 70 working days to grant or deny the GMP certification. The manufacturer can seek administrative re-consideration or administrative appeal.²²

In summary, the Proposed Regulations, together with the new pharmaceutical GMP regulations that became effective this year, represent the next step in ongoing efforts by the Chinese government to introduce stricter rules for pharmaceutical manufacturing. Pharmaceutical companies doing business in China should closely monitor these developments and be prepared to meet the additional requirements when the Proposed Regulations become effective. If you would like us to assist you to submit comments, or have any questions, please contact our China food and drug practice attorneys at:

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This information is not intended as legal advice. Readers should seek specific legal advice before acting with regard to the subjects mentioned herein. Only qualified PRC nationals working in PRC law firms are permitted to practice PRC law. Accordingly, as is true for all non-PRC law firms, we cannot express any legal opinion concerning the interpretation or application of PRC law. If a formal PRC legal

¹⁸ See Article 8, *Proposed Regulations*.

¹⁹ See Article 9, *Proposed Regulations*.

²⁰ See Article 10, *Proposed Regulations*.

²¹ See Article 21, *Proposed Regulations*.

²² See Articles 26 and 27, *Proposed Regulations*.

opinion is required in relation to any specific issues discussed in this memorandum, our practice is to arrange for such an opinion to be provided by one of our correspondent law firms in the PRC and to work closely with the PRC law firm in that exercise.

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