China Publishes Regulations on Medical Device GMPs and Inspection Requirements

by Steven J. Rizzi and Nathan A. Beaver

The State Food and Drug Administration of the People's Republic of China (SFDA) recently issued two interim regulations entitled Good Manufacturing Practice of Medical Devices (Interim GMP Regulations) and Good Manufacturing Practice of Medical Devices Inspection (GMP Inspection Regulations.) Both of these regulations will become effective on January 1, 2011. Companies doing business in China need to understand and prepare for implementation of these regulations.

GMPs are requirements that govern the methods used in, and the facilities and controls used for, the design, manufacture, packaging, labeling, storage, installation and servicing of all finished devices intended for human use. GMPs for medical devices are recognized as critical to maintaining quality control over the entire production process for medical devices and to ensure their safety and effectiveness.

As a result, GMPs have been adopted by the United States and other developed countries as the principal means for maintaining quality control for medical devices. Developed countries have not only taken quality control systems as an important prerequisite for medical devices entering into the marketplace, but also transitioned from a process involving only supervision of production prior to marketing (similar to the inspection process used by the United States Department of Agriculture for meat products – an inspector in the plant during the manufacturing process) to regulation of the overall production process – requiring controls in place for all aspects of design, development and manufacturing.

The United States implemented GMP regulations in 1978,[1] and enacted the Quality System Regulation (QSR) in 1996, which added design control requirements authorized by the Safe Medical Devices Act of 1990 as well as harmonized certain requirements with international standards set by the International Organization for Standards(ISO).[2] Japan instituted GMP requirements in 1999. The European Union has also implemented quality control requirements for medical device production.

The Need for Medical Device GMP and Inspection Regulations in China

China's medical device industry has developed rapidly in recent years -- there are now almost 13,000 medical device manufacturing companies in China. Increasing numbers of high-tech devices and combination devices have entered into the market during this time. China's rapid development of its medical device industry has created the need for more stringent requirements for the supervision of medical device manufacturers, especially with regard to quality control.

In 2000, the SFDA began the process of regulating the medical device industry in China through issuance of the "Method of Medical Device Manufacturing Enterprise Quality Assessment." These regulations served to eliminate small, workshop-type manufacturers without suitable production controls. However, the current manufacturing enterprise

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quality assessment system focuses only on examination of the finished device. Given the rapid development of the Chinese medical device industry, the Chinese government recognized the need for greater regulation to ensure quality control throughout the entire production process. The SFDA set out to implement medical device GMPs against this backdrop.

History of the SFDA GMP Regulations for Medical Devices

In 2003, the SFDA proposed promulgating Good Manufacturing Practices for Medical Devices. The SFDA noted that the GMP regulations would complement existing Chinese laws and regulations related to medical devices, and help to modernize China's regulatory system for medical devices to better serve the rapidly growing medical device manufacturing industry in China. SFDA also sought to draw upon other countries' experiences with GMPs for medical devices, as well as China's current GMPs for pharmaceuticals.

The recently published GMP Regulations have been in the works for more than five years, and were released following an extensive development process. In February 2004, the SFDA held a GMP drafting seminar and established a drafting group to begin the process. In January 2005, the Medical Device Bureau under the SFDA finished an initial draft of the General Provisions of the GMP Regulations. From March to July 2005, the SFDA organized several seminars and sent SFDA staff to different provinces and held seminars with provincial SFDA staff and representatives from medical device manufacturing companies.

In September 2005 the SFDA sent officials abroad to investigate and research international quality control systems. They conducted comparative research and exchanged opinions with experts who were familiar with the U.S. GMP regulations, Great Britain's quality control system and European quality control systems. At the end of 2005, the SFDA prepared comprehensive statistics and surveys on the status of medical device manufacturing companies' quality control systems nationwide. Based on a series of seminars, investigations and research studies, a draft of the GMP Regulations was finalized and published for public comment from May to July 2006.

During December 2006 to August 2007, the SFDA selected 10 relatively high risk medical device products, including disposable plastic blood bags, infusion sets, infusion pumps, plasma separators, orthopedic implants, cardiac pacemakers, catheters, intrauterine devices and hydroxyapatite implants. These products were used to carry out trials of the GMP Regulations in 45 medical device manufacturing companies located in eight different provinces, including Shanghai, Zhejiang, Guangdong, Shanxi, Beijing, Jiangsu, Sichuan and Tianjin.

This experience was extremely useful for making necessary modifications to the GMP Regulations. Based on the data collected from this experimental work, the SFDA made modifications to the draft GMP Regulations from September to December 2007, and began a draft of the GMP Regulations for Medical Device Inspection. During January to May 2008, the amended draft of the GMP Regulations was published a second time for public comment.

In March 2009, the SFDA requested that the provincial SFDA again solicit opinions, and held another seminar to examine the response to the amendment. On December 29, 2009, the SFDA issued the GMP Regulations, which will take effect on January 1, 2011.

China's GMP Regulations Stress Quality Control During the Entire Production Process

Overview

The GMP Regulations include 13 chapters with 69 articles:

- Chapter I General Provisions – requires that as part of quality control management, producers shall implement risk management procedures for the entire process of design, development, production, sale and servicing of medical devices;
- Chapter II Management Responsibility – dictates specific responsibilities for management;
- Chapter III Resource Management – specifies training and experience requirements for personnel responsible for production and quality control;
- Chapter IV Documentation and Record – specifies the types of documents that must be created and maintained for production management and quality control, including period for which records must be kept;
- Chapter V Design and Development – specifies requirements for product design and verification, product development, clinical trials and transition to production;
- Chapter VI Procurement – specifies controls concerning supplier quality control and the products they furnish;
- Chapter VII Production Management – discussed in detail below;
- Chapter VIII Monitor and Measure – procedures for establishing and implementing devices and processes

to ensure accurate monitoring and measuring of product requirements;
- Chapter IX Sale and Service – covers processes relating to sale, distribution, installation and service of medical devices;
- Chapter X Unqualified Product Control – requirements relating to identifying, assessing, handling and re-work of unqualified products;
- Chapter XI Customer Complaint and Adverse Event Monitoring – procedures for handling customer complaints, notifications and reporting;
- Chapter XII Analysis and Improvement – general procedures governing analysis of collected data relating to quality control and corrective actions concerning unqualified products and product recalls;
- Chapter XIII Supplementary Provisions – authorizes establishment of implementing rules for different classifications of medical devices and includes definitions of certain terms used in the regulations.

Focus on Quality Control

China's GMP Regulations focus on quality control requirements at each step of the production process. Provisions reflecting this focus include:

- Producers shall set up corresponding organizations and specify the responsibilities and powers of each organization in quality management;
- The person in charge of manufacturing department and the person in charge of quality management department shall not be the same;
- Producers shall establish and document a quality control system;
- The documents involved in the quality control system shall include the quality policy and quality objective, quality brochure, and procedure documents, technical documents, guidelines for production and records provided by the GMP Regulations, and other documents required by laws and regulations;
- Producers shall establish and document design control procedures for the design and development of medical devices;
- Producers shall establish and document monitoring and measuring control procedures, determine the required monitoring and measuring activities, and configure and control the corresponding monitoring and measuring devices;
- Producers shall establish and document an unqualified product control procedure, and specify the powers and responsibilities of the department and personnel in charge of unqualified product control;
- Producers shall identify, record, isolate and assess unqualified products, and take appropriate steps based on assessment of the unqualified products;
- Producers shall establish and document adverse event monitoring procedures in accordance with requirements for medical device adverse event monitoring and reappraisal management, define the responsibilities of an adverse event manager and specify collection methods, reporting rules, reporting procedures and deadlines concerning adverse events;
- Producers shall establish and document data analysis procedures, and specify data to be collected relating to product quality and operation of adverse event and quality control system processes, including market and supplier information.

Production Management

The most significant articles in the GMP Regulations concern production management. The requirements in this section are the most detailed:

- Producers shall devise and implement all production processes under their control;
- Producers shall formulate process guidelines, and define key and special processes;
- Producers shall use appropriate devices for production, processing, monitoring and measuring, and certify those devices under their control;
- Producers shall establish and maintain production records for each type of product;
- Production records shall meet retroactive requirements on medical devices, and include production and storage quantities;
- Producers shall establish and document product marking control procedures, and define appropriate methods to mark the products during the entire production process to identify and prevent mixed use and misuse of products.

The GMP Inspection Regulations Focus on High-Risk Devices

The GMP Inspection Regulations include seven chapters with 36 articles:

- Chapter I General Provisions;
- Chapter II Application and Material Examination;
- Chapter III On Site Inspection;
- Chapter IV Inspection Result;
- Chapter V Supervision and Inspection;
- Chapter VI Management on Inspectors;
- Chapter VII Supplementary Provisions.

The GMP Inspection Regulations focus on high risk devices, where the SFDA itself has responsibility for inspection of Class III medical devices with high risk. These include the following devices: heart pacemakers, artificial cardiac valves, intravascular stents and catheters, disposable plastic blood bags, animal source medical devices and allogeneic medical devices.

Inspection responsibility for other devices will fall on the "regulatory authorities of provinces, autonomous regions and municipalities," the so-called "Provincial SFDA." Only manufacturers of Class II and Class III devices must request and undergo inspection. Inspections can result in three scenarios: 1) passing inspection; 2) rechecking after rectification; and 3) failed inspection.

In the case of rechecking after rectification, manufacturers must resubmit an application for rechecking and submit a rectification report within six months. If after another inspection a passing certification is not obtained, the manufacturer will be deemed to have "failed." Those manufacturers failing inspection may re-file an application for inspection after six months.

The GMP Inspection Regulations state that inspectors should focus on the following items:

- Rectification of the items unqualified in the past inspection;
- Changes in the producer's organization, including the person in charge and other personnel in key positions;
- Changes in design and processing, main production equipment and test equipment, use and maintenance, and production environment;
- Product testing, especially entrusted testing conducted by third parties;
- Rectification of products deemed unqualified based on random inspections;
- Whether any commissioned or entrusted production meet relevant provisions;
- Report and handling of customers' complaints and adverse events;
- Other items provided by GMP Regulations and the implementing Rules.

Planning for Implementation of the New Medical Device Regulations

Overall, the medical device regulations do not appear to be inconsistent with U.S. GMP and QSR regulations. Thus, one would anticipate that companies already in compliance with U.S. regulations should not face significant issues complying with the China GMP regulations. Moreover, with limited exceptions, Chinese companies manufacturing only for foreign markets -- and not for the Chinese market -- are not subject to the regulations.[3]

Nevertheless, key to the new regulatory environment in China for medical devices will be the SFDA's approach to enforcement of the GMP and GMP Inspection Regulations. Because the GMP Regulations are not particularly detailed, much will be learned from the enforcement of the regulations by the Chinese authorities. Moreover, significant public events such as the past heparin recall, melamine recall and other food, drug and device safety issues involving Chinese food and drug manufacturers have the potential to alter the political climate in China and the degree of pressure placed on the SFDA to effect changes in industry practices. The highly publicized quality control problems in these other industries – and the resulting harm caused to the credibility of the corresponding regulatory agencies -- have no doubt sensitized the SFDA to the importance of proper regulation and oversight of the medical device industry.

Regardless, given the potential ramifications of the new regulations to the medical device industry in China, manufacturers with production facilities in China should keep a close watch on any further guidance provided by the SFDA in advance of the January 2011 effective date.

Max Lin, at Foley & Lardner's Shanghai office, helped to draft this article.

1 Under section 520(f) of the FDCA, FDA issued a final rule on July 21, 1978 prescribing CGMP requirements for medical devices. *See* 43 Fed. Reg. 31,508. This regulation became effective on December 18, 1978, and was codified under part 820.

2 *See* 61 Fed. Reg. 52,602.

3 According to SFDA officials, Chinese companies that manufacture condoms and glucose test strips for foreign markets must follow the China GMP Regulations even if not manufacturing for the Chinese market.