PREPARING FOR A U.S. FDA MEDICAL DEVICE INSPECTION

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**Introduction**

U.S. FDA is increasing quality system inspections of foreign medical device manufacturers. In this article we discuss the increase in frequency of inspections situations that manufacturers should avoid, the importance of FDA inspection preparation and two topics that should be covered in preparation for the FDA inspection.

In a recent report, U.S. FDA states that import of medical devices and radiation-emitting consumer products into the U.S. quadrupled during the period 2002–2010. It also referred to an independent report that stated that the number of medical device import lines has raised an average of 10% per year between 1998 and 2008 and now stands at 7.1 million lines per year. FDA states further that importation of medical devices is broad-based, spans all major device types and represents more than 35% of the U.S. medical equipment market.

The agency also notes that there is an important shift in the source of medical device imports. That is, a large proportion of U.S. medical product imports have historically come from Western Europe; however, between 2002 and 2009, imports from emerging markets such as Mexico, India, China and Thailand increased more rapidly than those from developed markets.

U.S. FDA predicts that this trend is likely to continue. This growth is having a direct impact on the agency’s product safety efforts, one of which includes an increase in quality system facility inspections of foreign medical device establishments. Over the last six months, manufacturers and others in several countries have noted a perceptible increase.

FDA’s investigators and inspectors visit more than 15,000 facilities a year, to ensure that products are manufactured according to current good manufacturing methods, and that they are labeled factually, following the FDA requirements for labeling. As part of FDA inspections, investigators collect about 80,000 domestic and imported product samples for examination by FDA scientists or for label checks.

**Inspection concerns**

When medical devices are cleared/approved for sale in U.S., manufacturers are informed that they are expected to comply with all applicable U.S. medical device requirements, including quality system requirements. Historically, FDA’s inspections of foreign medical device establishments were primarily postmarket inspections. Inspections of foreign establishments pose unique challenges to FDA, both in human resources and logistics. While FDA publishes its inspection guidelines, it does not make available to the public its inspection program indicating which medical device establishments it will inspect. FDA does not routinely inspect manufacturers of Class I devices, although it may inspect when there are areas of concern. U.S. FDA currently lacks adequate resources to inspect more than a small percentage of foreign manufacturers of Class II and Class III devices each year; however, it is adding more capability for inspections, as it recognizes the need to perform more inspections. As a result of past lack of resources, some foreign manufacturers have marketed their devices in the U.S. for many years without having been inspected by U.S. FDA and, in some cases, without ensuring compliance with the U.S. Quality System Regulation (21 CFR Part 820). Some of these manufacturers believe that conformity to the voluntary standard ISO 13485:2003, Medical devices—Quality Management Systems (QMS)—Requirements for regulatory purposes, will be sufficient to successfully pass a U.S. FDA facility inspection. They may also believe that ISO
quality system certification and surveillance audits are sufficient enough to prepare for FDA inspection. These assumptions are grossly incorrect. In the worst cases, the foreign manufacturer has been marketing its devices in the U.S. for years, but has not designed an adequate quality system under the U.S. FDA Quality System Regulation (QSR). Thus, the U.S. FDA inspection reveals that there is no reference to compliance with the QSR in the manufacturer’s quality system procedures. It may also be that the manufacturer has not recognized that U.S. FDA investigators and ISO quality system auditors sometimes have different interpretations or requirements that are common between the QSR and ISO 13485.

Inspection results

To illustrate where U.S. FDA inspections can differ from ISO 13485 assessments, the U.S. FDA inspection may show that U.S. requirements for adverse event reporting and corrections and removals have not been implemented. In the case of devices requiring servicing, there may be no process for analyzing service reports to identify trends indicating the need for corrective or preventive action. Another difference could be no procedure exists that requires service reports representing adverse events must be reported to U.S. FDA. When these and other types of problems are identified during an inspection, U.S. FDA issues findings referred to as Form 483. The manufacturer is then faced with serious issues that will need to be addressed in a brief period of time. That is, it will be necessary to gain a clear understanding of the requirements that have not been met, determine an effective and convincing corrective and preventive action plan, and respond in writing, in English, to U.S. FDA, addressing the problems identified during the inspection, generally within 15 working days of the inspection.

This is a tremendous burden on a manufacturer who needs to meet routine production and operation schedules and, at the same time, dedicate adequate resources to addressing U.S. FDA inspection findings and responding in writing. An inadequate response can result in a Warning Letter, which may or may not include an order to cease importing affected devices into the U.S. until corrections are made and, in some cases, until a follow-up inspection is scheduled.

Although an inspection, or any quality system audit, can result in the identification of one or more quality deficiencies, awareness that specific attention needs to be paid to the QSR and institution of an inspection preparation program before being notified by U.S. FDA of an imminent inspection can prevent serious compliance problems.

U.S. FDA inspection preparation

FDA generally notifies manufacturers about a week in advance of postmarket quality system inspections of domestic establishments and about 6 to 8 weeks in advance of postmarket quality system inspections of foreign establishments.6

Preparing for a U.S. FDA inspection should be an organized activity involving all company personnel performing work covered by the QSR, including executive (top) management, design and development, production, quality control, quality assurance, warehouse, purchasing, human resources, packaging, distribution, information technology, and perhaps, others.

These are some of the topics that companies should consider covering during such a preparation:

• Basic regulatory framework upon which U.S. FDA inspections are based—the inspection process is based on U.S. law, which differs in significant ways
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from European quality system audits conducted by Notified Bodies;7

• U.S. FDA regulations and requirements that will be examined during the inspection, which is not limited to the QSR;

• QSR provisions that differ from ISO 13485, the U.S. FDA inspection process;

• Careful review of the U.S. FDA Quality System Inspection Technique (QSIT) document,8 that is used by investigators as the basis for medical device facility inspections;

• Actions to take before, during and after the inspection;

• Behavior during an inspection, including behavior that should be avoided.

It is important to note that materials that can be used to develop such an inspection preparation program are readily available from many sources, including online, most notably from the U.S. FDA website (www.fda.gov).

Basic regulatory framework

The U.S. Food, Drug & Cosmetic Act (FD&C Act) is a set of laws providing U.S. FDA with the authority to ensure:

• The safety of all food except for meat, poultry and some egg products,

• The safety and effectiveness of all drugs, biological products (including blood, vaccines and tissues for transplantation), medical devices, and animal drugs and feed,

• Cosmetics and medical and consumer products that emit radiation do no harm.

The FD&C Act prohibits certain acts, including the introduction or delivery for introduction into U.S. interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded. A medical device is adulterated if it:9

• Is subject to a performance standard and does not comply with all the requirements of the standard;

• Is a Class III device and fails to conform to the requirements for an approved premarket approval application or a notice of completion of a product development protocol;

• Is in violation of good manufacturing practice requirements as specified in the QSR;

• Fails to comply with an Investigational Device Exemption (IDE);

• Fails to comply with other requirements against adulteration in Sec. 501 of the FD&C Act.

A medical device is misbranded if:

• Its labeling is false and misleading,

• It is commercially distributed without U.S. FDA concurrence on a Section 510(k) submission,

• It fails to comply with other requirements against misbranding in Sec. 502 of the FD&C Act.

It is important for manufacturers to understand that under U.S. regulations and requirements, “labeling” includes the device label and any other written, printed or graphic material that accompanies a device and any of its wrappers or containers, plus its operating and servicing instructions.10 This can include Internet descriptions, information given by sales people, and convention displays.

Regulations covered during a U.S. FDA inspection

Manufacturers should avoid the misconception that U.S. FDA inspections consist only of an assessment of QSR compliance. Inspections also examine
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Manufacturers should always ensure that their establishment registration and device listings are current. The manufacturer of a tracked device also should ensure that U.S. importers and distributors are fulfilling the requirements in 21 CFR Part 821, because failure to comply with tracking requirements may cause the device to be detained at the U.S. point of entry. The firm should update the listings and verify that their listings are up-to-date every six months and update them if they are not. The firm should renew its annual registration as required by 21 CFR Part 807.

**Final thoughts**

Preparing for an impending FDA inspection is like preparing for a suddenly announced visit from new in-laws. Knowing what to expect can save hours of anxiety, headache and heartburn.

UL can provide training using the same content used for training FDA Inspectors, conduct the pre-inspection or gap assessment audit to help the manufacturer prepare for the actual audit and provide on-site support during an FDA inspection. Pre-inspection benefits the manufacturer in that it provides personnel with a real experience of how an FDA inspection will take place and UL’s report containing inspection findings will help improve the adequacy of the sub-systems so that the identified problems do not arise during a real FDA inspection.

Many valuable lessons will be learned in how to prepare for and manage an inspection by FDA, ensuring manufacturer/company reduces the potential for the issuance of damaging FDA Form 483s and associated Warning Letters that can seriously disrupt business and profitability.

*So, are you ready?*
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References:
2. USA Medical Device Market Intelligence Report, Quarter III, 2010, Espicom Business Intelligence
6. GAO, FDA Faces Challenges in Conducting Inspections of Foreign Manufacturing Establishments (May 2008)
10. http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/GeneralandSpecialControls/ucm055910.htm#false_or_misleading_labeling

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