

Preparing for a US FDA Medical Device Inspection, Part 1

US FDA is increasing quality system inspections of foreign medical device manufacturers. Part 1 of this article discusses why this is occurring, situations that European manufacturers should avoid, the importance of US FDA inspection preparation and two topics that should be covered in inspection preparation. Part 2, which will be published in the May/June issue, will discuss additional preparatory measures to take in anticipation of an inspection.

In a recent report,¹ US FDA states that imports of medical devices and radiation-emitting consumer products into the United States quadrupled during the period 2002–2010. It also referred to an independent report² that stated that the number of medical device import lines has risen an average of 10% per year between 1998 and 2008 and now stands at 7.1 million lines per year. US FDA states further that importation of medical devices is broad-based, spans all major device types and represents more than 35% of the US 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 US 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. US 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. This article concentrates on European manufacturers operating under the European directives for medical devices who are also marketing their devices in the United States.

Worst-case scenario

When medical devices are cleared or approved for sale in the United States, manufacturers are informed that they are expected to comply with all applicable US medical device requirements, including quality system requirements. However, US FDA does not make available to the public its inspection programme indicating which medical device establishments it will inspect. It is also common knowledge that US FDA lacks adequate resources to inspect more than a small percentage of foreign manufacturers of Class II and Class III devices each year. As a result, some foreign manufacturers have marketed their devices in the United States for many years without having been inspected by US FDA and in some cases without ensuring compliance with the US 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—Requirements for regulatory purposes, will be sufficient to successfully pass a US FDA facility inspection. They may also believe that ISO quality system certification and surveillance audits are sufficient preparation for an inspection by the US agency.

These assumptions are grossly incorrect.

In the worst cases, the foreign manufacturer has been marketing its devices in the United States for years, but has never paid any attention to the QSR. Thus, the US FDA inspection reveals that there is no reference to compliance with the QSR

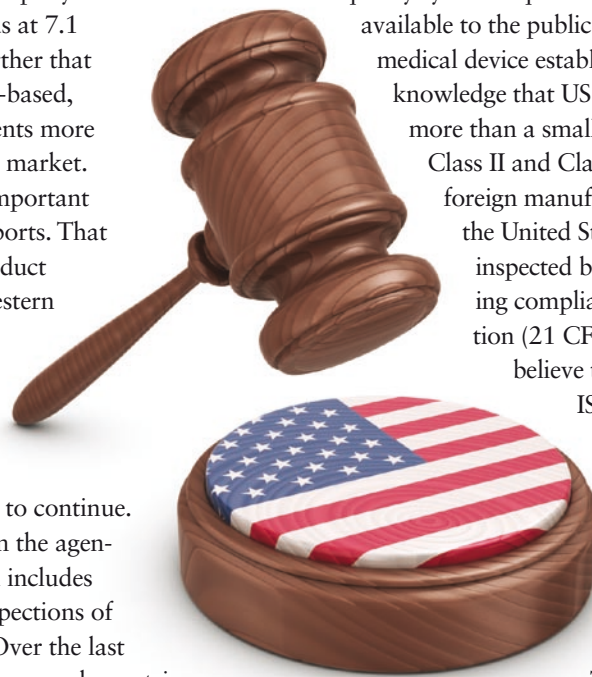
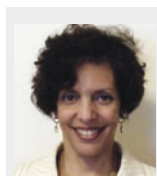


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in quality system procedures and it is evident that no check of the QSR for quality system requirements, which are not included in ISO 13485, has been made. It may also be that the manufacturer has not recognised that US FDA investigators and ISO quality system auditors sometimes have different interpretations of requirements that are common to the QSR and ISO 13485. As examples, the US FDA inspection may show that US requirements for adverse event reporting and corrections and removals have not been implemented; or, in the case of devices requiring servicing, there may be no process for analysing service reports to identify trends indicating the need for corrective or preventive action; or no procedure requiring that a service report representing an adverse event must be reported to US FDA. When these and other types of problems are identified during an inspection, the manufacturer is 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 US 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 address US FDA inspection

findings and respond 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 United States 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 programme before being notified by US FDA of an imminent inspection can prevent serious compliance problems.

US FDA inspection preparation

Preparing for a US FDA inspection should be an organised 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 US FDA inspections are based—the inspection process is based on US law, which differs in significant ways from European quality system audits conducted by Notified Bodies;
- US FDA regulations and requirements that will be examined

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- during the inspection, which are not limited to the QSR;
- QSR provisions that differ from ISO 13485;
 - the US FDA inspection process;
 - careful review of the US FDA Quality System Inspection Technique (QSIT) document,³ which is used by investigators as the basis for medical device facility inspections;
 - actions to take before, during and after the inspection;
 - behaviour during an inspection, including behavior that should be avoided.

The first two topics are discussed below. Part 2 of this article will cover the remaining topics. It is important to note that materials that can be used to develop such an inspection preparation programme are readily available from many sources, including online, most notably from the US FDA website (www.fda.gov).

Basic regulatory framework

The US Food, Drug & Cosmetic Act (FD&C Act) is a set of laws providing US 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,

- that 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 US interstate commerce of any food, drug, device, or cosmetic that is adulterated or misbranded. A medical device is adulterated if it:

- 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 labelling is false and misleading,
- it is commercially distributed without US 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 European manufacturers to understand that



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under US regulations and requirements, “labelling” 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.


Regulations covered during a US FDA inspection

Manufacturers should avoid the misconception that US FDA inspections consist only of an assessment of QSR compliance. Inspections also examine compliance with the following regulations:

- Medical Device Reporting (MDR) (21 CFR Part 803)
- Corrections and Removals (21 CFR Part 806)
- Establishment Registration and Device Listing (21 CFR Part 807)
- Medical Device Tracking, where applicable (21 CFR Part 821)

In addition, Electronic Records and Signatures (21 CFR Part 11) may be evaluated; however, inclusion of this regulation in the inspection is highly variable, in part because US FDA is re-examining its policies and requirements related to this regulation.

Some European manufacturers fail to develop procedures to ensure that MDR requirements are met because they assume that the US importer alone is responsible for US adverse event reporting. This is incorrect. The MDR regulation applies to all manufacturers, including foreign manufacturers. The responsibilities for submitting MDRs were discussed in a previous article.⁴ A similar error is sometimes made regarding compliance with corrections and removals. Although the European manufacturer or the US importer can submit corrections or removals reports to US FDA, the manufacturer needs to ensure that proper procedures have been implemented to comply with these and other US importer requirements. Failure to do so could jeopardise the regulatory compliance status of the device and, in serious cases, the continued import of the devices into the United States.

European manufacturers should always ensure that their establishment registration and device listings are current. The European manufacturer of a tracked device also should ensure that US 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 US point of entry. 

References

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