

Preparing for a US FDA Medical Device Inspection, Part 2

US FDA is increasing quality system inspections of foreign medical device manufacturers. Part 1 of this article discussed 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 covers additional preparatory measures to take in anticipation of an inspection.

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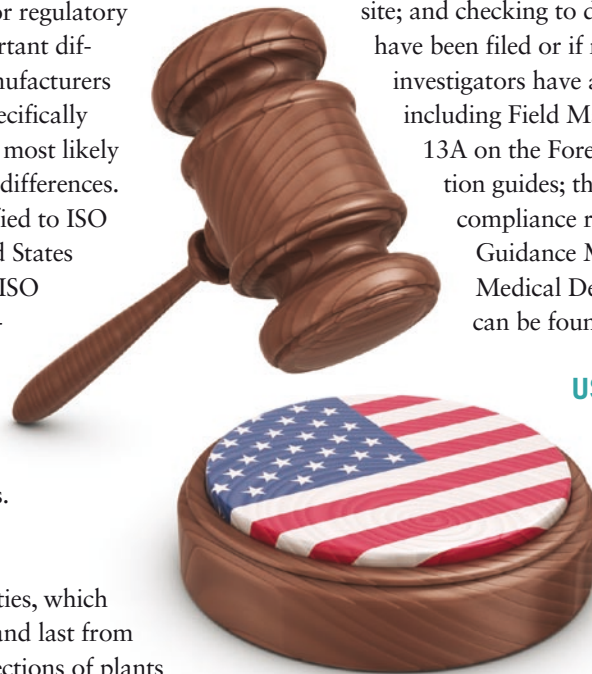
There is considerable overlap between the provisions of the US Quality System Regulation (21 CFR Part 820; QSR) and ISO 13485:2012, Medical devices—Quality management systems—Requirements for regulatory purposes. However, there are also important differences.¹ European medical device manufacturers with internal audit programmes that specifically cover the provisions of the QSR are the most likely to effectively identify and address these differences.

Unfortunately, some companies certified to ISO 13485 that market devices in the United States limit their internal quality audits to the ISO 13485 provisions or departmental operating procedures. When this approach is taken, QSR requirements that differ from ISO 13485 are missed, leading to a failure to comply with the QSR and its internal audit requirements.

US FDA inspection process

In contrast with inspections of US facilities, which may involve one or more investigators and last from days to weeks to months, US FDA inspections of plants outside the United States generally involve one investigator and last three to five days. When US FDA has identified a non-US firm for inspection, it contacts the firm's US agent or may contact the firm directly. The time that elapses from this first contact to the actual inspection can vary, but it's usually several weeks.

Investigators prepare for inspections by checking the establishment's registration and device listing in the US FDA database; reviewing previous establishment inspection reports (EIRs) of the site; and checking to determine if any medical device reports have been filed or if recalls have been conducted. In addition, investigators have access to a number of guidance documents, including Field Management Directives (FMD), such as FMD 13A on the Foreign Inspection Program; a variety of inspection guides; the Investigation Operations Manual; and compliance references, such as the Compliance Program Guidance Manual (CPGM) 7382.845, Inspection of Medical Device Manufacturers. All of these documents can be found on the US FDA website, www.fda.gov.



US FDA Quality System Inspection Technique

The Quality System Inspection Technique (QSIT)² is intended to help US FDA investigators conduct efficient inspections and reduce, as much as practicable, inspection time. QSIT is based upon the inspection of four major QS subsystems:

- Management Controls,
- Design Controls,
- Corrective and Preventive Actions (with its satellite programmes of Medical Device Reporting, Reports of Corrections and Removals and Medical Device Tracking),

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Consulting, a full service European CRO and international consultancy company that provides regulatory, quality and European Authorised Representative services to life science companies.

■ Production and Process Controls (with its satellite programme of Sterilization Process Controls).

Companies should use the QSIT guide to prepare responses to the questions that the guide directs investigators to ask.

A range of “Compliance Program Manuals,” which cover all US FDA-regulated areas, can be found on the agency’s website.³ One such manual is the aforementioned CPGM 7382.845. This is an important document for companies preparing for US FDA inspections, because it includes aspects of the inspection process, such as administrative and enforcement activities, that are not covered in the QSIT guide.

Before the inspection

An important part of every US FDA inspection is a check of company quality records to assess whether or not a company is in compliance with its own standard operating procedures (SOPs) and work instructions. Some companies have not previously experienced such an in-depth review of their records and may be unprepared for this very detailed activity. It is therefore highly advisable

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that a thorough internal check of quality records is carried out before the inspection.

The roles of key personnel should be clearly determined before the inspection. For example, the company should identify the most responsible person at the facility, which is generally the CEO, COO, general manager or similarly responsible person. The principal contact with whom the investigator will interact during the inspection, usually the person responsible for quality assurance, should also be identified. Someone should also be designated to take notes and ensure that documents requested by the investigator are provided in a timely fashion. Various subject experts and persons who can retrieve requested documents should also be identified and be available for the entire inspection.

A meeting room should be made available, with local access to a photocopier. A copy of the same information that the investigator is likely to have accessed in preparation for the inspection should also be assembled, such as a list of 510(k)s and PMAs, plus establishment registration and device listing data. If a company has been inspected previously, the Establishment Inspection Report (EIR) should be obtained and reviewed, as well as any Form FDA 483 observations, Warning Letters and other correspondence between

the company and US FDA. It is critical to ensure that all noncompliance issues identified in this correspondence have been addressed and that there are no pending matters.

A “back office” should be established with personnel who can ensure that requested documents are made available without undue delay. A list should be maintained of all documents reviewed by the investigator or a copy of the cover sheet should be made. If the investigator requests a copy of a document, two copies should be made, so that one copy can be retained. Confidential documents or content should be clearly marked. The investigator expects to see originals of some documents, such as device history records, and the investigator should always be informed when being provided with originals.

During the inspection

During the opening meeting, the investigator should be asked whether a presentation on the company can be made. If the investigator agrees, the presentation should include information such as a brief company history, number of employees, working hours, number of work shifts and shift hours, a list of devices being marketed in the United States and their 510(k)/PMA references, the establishment registration number, device listing information and percent exported to the United States. It should be no more than 15 or 20 minutes and should not be a sales or marketing presentation. A site diagram should be included or a paper copy provided, showing the location of the main offices and manufacturing areas.

The manner in which personnel respond to questions from the investigator and the clarity of the answer will have an important effect on the inspection process and possibly on the outcome. Staff should therefore be briefed that when the investigator asks a question, they should listen carefully and allow the investigator to complete the question before responding. The response should always be relevant to the question. For example, if the investigator asks for a description of the CAPA system, do not automatically provide a copy of the procedure. Describe the process. If the investigator wishes to see the procedure, he or she will ask for it.

If the investigator identifies important deficiencies during the inspection, they will be listed on a Form FDA 483, Inspectional Observations, and the investigator will read the Form FDA 483 observations during the closing meeting. The company will be asked if it wishes to make any comments to be recorded on the form. If the investigator makes verbal comments, suggestions or describes nonconformities not reported on the Form FDA 483, the company should note these for internal discussion after the inspection. This is because these comments and minor observations may be included in the EIR and could be checked in a subsequent inspection.

Inspection behaviour

Personnel should be briefed to be honest when answering questions from the investigator and avoid behaving in a defensive or aggressive manner. They should understand that mistakes or omissions

can occur, but dishonesty can lead to very serious problems during an inspection. Personnel should not argue with the investigator. If it is not possible to convince the investigator of a particular point, ensure that someone has made notes of the discussion and address it later during the company strategy meeting.

After the inspection

After the inspection, the investigator will complete the EIR and submit it to the relevant US FDA office(s) for review. Any observations on the Form FDA 483 or comments made by the investigator should be addressed using the company CAPA system. If a Form FDA 483 has been issued, it is important to complete the response letter within 15 business days, providing relevant updates within reasonable timeframes, otherwise there is a risk of receiving a Warning Letter or other enforcement action. All communications with US FDA must be in English.

Unfortunately, some companies make serious mistakes when responding to a Form FDA 483, which can also lead to a Warning Letter. One of the most common mistakes is a failure to provide objective evidence of a corrective or preventive action. That is, when corrective or preventive actions have been completed—revised SOPs, completed quality forms or training records, for example—they should be provided in the response. When objec-

tive evidence is not yet available, the corrective action to be taken should be described clearly, along with the timeline for providing the objective evidence to US FDA. Commitments should never be made to provide such evidence if it is clear that the stated deadlines cannot be met.

The benefits of being prepared

Effective US FDA inspection training and preparation programmes can greatly enhance the chances of an inspection going smoothly; however, companies are unlikely to escape without any deficiencies being noted unless QSR requirements have been fully covered within the quality system. ☺

References

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2. FDA Guide to Inspections of Quality Systems, Quality System Inspection Technique (August 1999) www.fda.gov/downloads/ICECI/Inspections/UCM142981.pdf.
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