What to expect during a US FDA medical device inspection

How the QSR inspection is structured, creating a pre-audit checklist, and how to follow up on findings

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October 2023

Time for inspection

Preparing for FDA and MDSAP inspections

How the MDSAP program impacts the Quality System Inspection Technique (QSIT), how to participate and follow up on findings, and the impending incorporation of ISO 13485:2016 Medical devices – Quality management systems into the Quality System Regulation

The U.S. Food and Drug Administration (FDA) participates in the Medical Device Single Audit Program, which impacts how the Quality System Inspection Technique (QSIT) is implemented in routine and non-routine inspections. MDSAP was implemented by the International Medical Device Regulators Forum (IMDRF) with five international partners:

- Therapeutic Goods Administration of Australia
- Brazil's Agência Nacional de Vigilância Sanitária
- Health Canada
- Japan's Ministry of Health, Labour and Welfare, and the Japanese Pharmaceuticals and Medical Devices Agency
- U.S. Food and Drug Administration

MDSAP Audits are performed by recognized Auditing Organizations (AOs) and are structured using ISO 13485:2016 as the quality system basis, while adding on country-specific requirements. After a three-year pilot program to test the success of the program, the FDA determined that the MDSAP audit reports would be accepted as a substitute for routine agency inspections. The FDA hosts and maintains web pages for the MDSAP documents[1]:

Here, policies, procedures, templates and forms can be located. These provide the tasks that AOs use for conducting audits. The audit approach consists of the following:[2]

- Chapter 1 – Management (11 tasks)
- Chapter 2 – Device Marketing Authorization and Facility Registration (three tasks)
- Chapter 3 – Measurement, Analysis and Improvement (16 tasks)
- Chapter 4 – Medical Device Adverse Events and Advisory Notices Reporting (two tasks)
- Chapter 5 – Design and Development (17 tasks)
- Chapter 6 – Production and Service Controls (29 tasks)
- Chapter 7 – Purchasing (12 tasks)

In addition, six annexes cover specific information related to (1) auditing product/process-related technologies and technical documentation, (2) auditing requirements for sterile medical devices, (3) medical device adverse events and advisory notices reporting processes (timelines), (4) expectations for written agreements for regulatory purposes, (5) Japanese quality management system (QMS) revisions and relationships and (6) acceptable exclusions from scope of certification.

The audit framework includes a Stage 1 documentation review and evaluation of preparedness for the Stage 2 audit. Stage 2 involves a complete evaluation of QMS implementation and effectiveness and will use all the MDSAP audit process tasks as applicable to the organization. MDSAP audits are scheduled with the AO contracted by the organization to perform the audits.

The MDSAP audit sequence follows a process approach and has four primary processes:

- Management process
- Measurement, Analysis and Improvement process
- Design and Development process
- Production and Service Controls process with links to the Purchasing process

The MDSAP audit process has two additional supporting processes: Device Marketing Authorization and Facility Registration and Medical Device Adverse Events and Advisory Notices Reporting. These processes are necessary to fulfill specific requirements of the participating MDSAP regulatory authorities.

The FDA reserves the right to inspect if there are areas of concern highlighted in the MDSAP audit report or for other types of inspections, such as inspections for pre-market approval, follow-up, or for-cause inspections.

For those types of inspections, FDA inspectors will audit in accordance with the QSIT. In addition, for manufacturers who are not in the MDSAP program, FDA still uses the QSIT for inspections. In these types of inspections, the FDA will provide U.S.-based companies with some advance notice, usually two to five business days.

Picture a scenario where you are busily answering emails and then the phone rings. The person on the other line is with the local FDA office, letting you know that they will be at your facility in the next few days to perform an inspection. This notice is meant to give time to prepare for the arrival of the inspector. If the system is not fully compliant, this is likely not enough time to correct all deficiencies. However, it does allow you to prepare logistically. More about that later. If your company is outside of the United States, you usually have a bit more time, as the FDA will plan the inspection around others in the area and will need to prepare travel plans.

This paper will suggest activities leading up to the inspection, what to expect during an inspection, and what a company should do after the inspector leaves the facility. Hopefully, these suggestions will help dispel inspection fears and prepare the organization to be inspection-ready. Of course, these preparations also apply to MDSAP inspections.

Regulatory requirements

The first aspect we should discuss is the actual set of requirements a company would be expected to comply with regarding manufacturing and distributing a finished medical device. For the FDA, the primary regulation that must be followed is the Code of Federal Regulations Title 21 CFR 820, **Quality System Regulation (QSR)**[3]. However, there are other regulations that must be followed and are often forgotten as manufacturers are concentrating on QSR requirements. These include the following:

- **21 CFR 801**, Labeling
- **21 CFR 803**, Medical Device Reporting
- **21 CFR 806**, Reports of Corrections and Removals
- **21 CFR 807**, Establishment Registration and Device Listing
- **21 CFR 809**, In Vitro Diagnostic Products for Human Use
- **21 CFR 810**, Medical Device Recall Authority
- **21 CFR 830**, Unique Device Identification

All these regulations must be followed as applicable to the organization. When the phrase “as applicable” is mentioned, this relates to the fact that throughout the regulations there may be requirements that are not applicable or appropriate for an organization. As an example, if an organization distributes a single-use device, then servicing of the device, i.e., 21 CFR 820.200, would not be applicable. It is important that organizations understand the application of the FDA regulations and compliance expectations when adhering to these regulations.

It is also important to recognize that on Feb. 23, 2022, the FDA announced a proposed rule, Quality System Regulation Amendment, which would primarily incorporate by reference ISO 13485:2016 into the medical device regulation. While the proposed regulation will incorporate ISO 13485:2016 as the foundational quality management system requirements, the additional FDA-specific requirements will remain intact. Furthermore, the QSIT will remain in place for FDA inspections, revised as applicable to incorporate the requirements of the proposed rule.

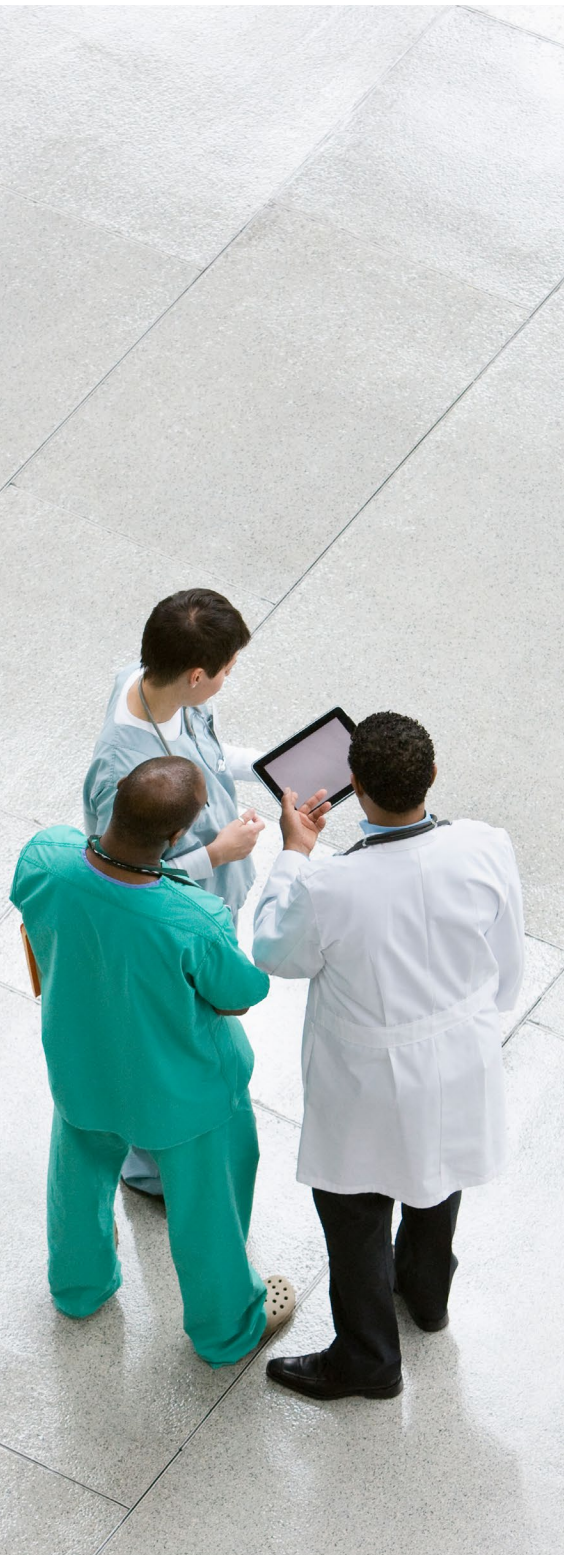
Inspection technique

The FDA developed the QSIT[5] methodology for performing inspections during the release of the QSR regulations in 1996. The QSIT guide, which is to be used in conjunction with the various compliance program guides, regulations, and guidance documents, provides a foundation for performing QSR inspections.

FDA designed the QSIT as a “top-down” approach; it focuses on the organization’s entire quality system to identify potential quality issues within the company.

The QSIT focuses on four major subsystems of the quality system shown below that establish the basis for an FDA investigator to review procedures, processes and quality records. The FDA published the QSIT guide to demonstrate what they will review during an inspection: therefore, organizations should read and study the QSIT guide and apply its principles when they review and audit their quality system.

FDA QSR Subsystems
Management Controls: Quality Manual, Quality Policy, Quality Planning, Management Commitment, Management Reviews, Training and Personnel, Internal Audits
Corrective and Preventative Action (CAPA): Sources of Data, Nonconformities, Customer Complaints, Medical Device Reporting, Follow-up Activities
Design Controls: Design Planning, Design Inputs, Design Outputs, Verification, Validation, Risk Management, Design Reviews, Device Master Record
Production and Process Controls: Product Realization (Device Master Record), Manufacturing, Process Validation, Calibration, Identification, Traceability, Device History Record, Labeling, Packaging, Storage, Delivery, Servicing



Always be prepared

One of the most effective ways to support a successful FDA inspection is to always be inspection-ready. Even though the FDA generally pre-announces inspections, a few days or even a few weeks are not enough time to correct fundamental compliance issues in a quality system. This is the reason why a medical device manufacturer should always be inspection-ready, which follows the main theme that procedures have been established and successfully implemented, records are being maintained to show conformance and, when applicable, that issues identified are being corrected.

The primary method for accomplishing this is to have a robust internal audit program. Emergo by UL frequently advises organizations to utilize their internal audit process to locate quality system problems first rather than letting FDA inspectors find them. These services are also available and helpful for preparing for MDSAP inspections. Even though these inspections are scheduled each year, having the assistance of an outside party can augment the preparation process.

Confirm that the internal audit program is unbiased and that personnel in the organization are forthcoming when describing their processes. Personnel should be trained in the internal audit process, and its value in continuous improvement of the quality system. The worst cases arise when personnel hide issues from their internal auditor because they do not want to get reprimanded. This helps no one when the FDA identifies these issues during an inspection. Mock audits that mimic FDA inspections can help uncover fundamental compliance issues.

Never be surprised — know where the skeletons are buried. All companies have events/mistakes or documentation that they are not proud of, but hopefully these have been addressed and not repeated. Auditors/inspectors have a way of finding these, so be prepared to address them confidently: “Yes, we know, and here’s what we did to mitigate this. Here’s why there is no risk to the product, and here’s the corrective action.”

Another good method is to have your quality system periodically reviewed by an independent third party, as internal auditors may get too close to their own quality system. As Benjamin Franklin said, “By failing to prepare, you are preparing to fail.” The best method for a successful inspection is to always be prepared.

Before the inspection

Assuming your quality system is in good shape and your internal audit procedure is followed closely, you may be wondering what to do once you receive the first call from the FDA. You may not have much time to prepare for the investigator's arrival but don't panic. Refer to the U.S. FDA Audit Checklist at the end of this paper for a step-by-step pre-audit checklist.

For MDSAP inspections, a good tool for preparation is to use the MDSAP audit model that the FDA includes on its webpage: MDSAP Medical Device Single Audit Program Audit Approach, Document No. MDSAP AU P0002.[6] This document provides insight into the tasks that auditors will use when auditing to the MDSAP and includes country-specific requirements, which allows companies to tailor their internal audit program for the countries they include in the MDSAP audits they will undergo.

During the inspection

The company should have a procedure whereby an inspection coordinator or an individual to escort auditors is identified to guide the inspection and answer the main questions when inspectors arrive at the facility. This individual should be knowledgeable about the organization. A room should be designated for such opening meetings, which should be attended by pertinent personnel and management. After the opening meeting, the organization should provide an overview of the company and its operations. This helps inspectors orient to the business conducted at the site. Typically, a tour of the facility will be included before the nuts and bolts of the inspection begin. It is best practice to have a tour route determined prior to the audit, and any operations/personnel visible to the inspectors should be forewarned.

Once introductions have been made and background information on the organization has been described, the investigator gets right to business by requesting documentation, commonly referred to as objective evidence. Quality records must support the manufacturer's ongoing activities, support how the procedures are written, and show that the processes have been implemented. The bulk of the inspection activity involves the investigator asking for a procedure, interviewing personnel, asking questions about the process, and reviewing records that are generated across all facets of the quality system.

If this is a full QSIT inspection, the inspector will generally cover each of the four major subsystems of the QSIT, at a rate of approximately one per day. An example of inspection flow is shown in Figure 1. It is important to understand that for domestic inspections (those performed in the United States), an FDA inspector can extend the time required for the inspection if they observe quality issues that need further investigation. If the audit is not a full audit, generally, two of the subsystems will be chosen by the FDA for audit.

Day 1	Day 2	Day 3	Day 4
• Facility Entry • Introductions • Opening Meeting • Management Controls	• Corrective and Preventive Action • Customer Complaints • MDR Report	• Production and Process Controls • Sterilization Processes • Validations	• Design Controls • Closing Meeting • (Issuance of Form 483)

Basic flow of an FDA inspection over four days — note this is just an example as each investigator may shift the subsystems around or take more time per subsystem.

MDSAP audits are based on a three-year audit cycle. The initial certification audit is a complete audit of the quality management system. The initial audit is followed by a partial surveillance audit in each of the following two years, and a complete re-audit/certification in the third year. The audit schedule is provided by the AO prior to the audit. In FDA or MDSAP audits, the inspector must collect a sampling of documents and records, which must be readily available. For this reason, setting up a back room to manage document requests and keep records of documents provided is highly recommended. A notetaker should be appointed to maintain a record of proceedings.

To prepare for an inspection, your internal audit program should challenge the documentation system, ensuring documents can be provided in a timely manner.

The FDA inspector should follow the process from the QSIT guide, but if they discover quality issues during the inspection, then this may lead to a much more detailed review of specific aspects of the product quality and/or the quality system.

Most frequent Form 483 observations
Corrective and preventive action, 21 CFR 820.100: Lack of/inadequate procedures
Customer complaints, 21 CFR 820.198: Lack of/ inadequate procedures
Process validation, 21 CFR 820.75: Lack of/ inadequate validations
Purchasing controls, 21 CFR 820.50: Lack of/ inadequate procedures
Nonconforming product, 21 CFR 820.90: Lack of or inadequate procedures
Medical device reporting, 21 CFR 803: Lack of/ written MDR procedures

The auditors' purpose is to assess compliance with the QSR or MDSAP requirements as applicable. The FDA publishes metrics identifying problem areas of quality system compliance annually on its website. The list in the sidebar sums up areas that continually receive the most observations during FDA inspections[7] as listed on FDA Form 483.

According to SAI Global, the three most common nonconformances found when conducting MDSAP audits are[8]:

- Document control and documentation errors
- Risk management and risk-based thinking
- Purchasing and supplier control

Medical device manufacturers can expect that these areas will be continually reviewed with more scrutiny by inspectors. This should prepare an organization for concentrating its efforts and resources on ensuring that these processes are fully compliant within the organization.

Exit/closing meeting

Inspectors conduct a closing meeting with the organization that summarizes the inspection findings. The FDA will issue an FDA Form 483 and AOs will issue a recap of findings based on a grading sheet used for MDSAP findings[9]. These will list objectionable findings made during the inspection. The list of observations will be reviewed in the closing meeting by the auditors to determine that there is no clarification required and to give the company an opportunity to discuss them as necessary.

Timelines for responses will be addressed in the closing meeting. The observation(s) can be annotated to state what the company promises to correct as part of their response.

What to do afterward

If the organization has received an FDA Form 483 with objectionable items listed, it is imperative that a response is sent to the FDA within 15 calendar days. For MDSAP responses, the timelines may vary, depending on the gravity of the findings. The FDA has often commented in public forums that if a response is not received within the required timeframe, then a Warning Letter will be issued. Responses to the observations must be clearly addressed in detail, describing the plan for correcting the items.

A basic structure of the response process is shown in the sidebar, including the content currently expected by the FDA. Deficiencies in the response, including missing information, not providing supporting records, or lacking true commitment to making the corrections, may result in a Warning Letter from the FDA, or unfavorable follow-up action by the MDSAP auditing organization. FDA Warning Letters are publicly posted on the FDA website[10], allowing customers and, more importantly, competitors, to see deficiencies in your quality system.

There is usually no negotiating the content of a Form 483 or Warning Letter after it has been issued, so it is important for an organization to stay continually vigilant in the compliance of their quality system.

Steps to address FDA Inspection observations
Correction: Actions taken immediately to correct an observation
Root cause analysis: Identify the true root cause; utilize root cause analysis tools such as the Five Whys
Retrospective review: Review the activities not just related to the observation, but what is being done to review information in the past
Corrective action plan: Actual corrective action that is short or long term to remove the nonconforming situation
Effectiveness check: Describe how the organization will assure the correction is sufficient
Timeline: When all the activities are to be completed

Note that MDSAP audit reports go to all the regulatory authorities, so the FDA could also act on a poor MDSAP audit report, which could result in the FDA performing their own inspection.

After 60 days, the organization should put in a request through the **Freedom of Information Act**[11] to receive a copy of the Establishment Inspection Report (EIR). This is a narrative created by the FDA investigator that details what was reviewed, the persons interviewed and comments made during the inspection. This should always be obtained after an inspection is performed to understand any implications or significant comments made regarding an observation by the investigator.

U.S. FDA Audit Checklist

U.S. FDA and MDSAP Audit Checklist	
☐ Notify all staff and employees.	Inform your entire staff that an audit is coming and the dates the inspector will be on-site. Assure that the key individuals are available during the inspection or identified as designated individuals.
☐ Distribute external audit procedures to key staff.	If you already have a procedure for handling inspections, your employees should be familiar with the inspection process. However, provide them with a review of the external audit procedure to avoid any surprises.
☐ Reserve audit space and equipment.	Designate a space on-site for the investigator to conduct the inspection, such as a large office or conference room. Consider a secondary room as a backroom for preparing material for the investigator.
☐ Designate an Inspection Coordinator.	Identify a member of your staff to be the inspector's point of contact while they are on-site. This person should be a senior member of your quality team, so they are familiar with your organization and able to answer main questions.
☐ Block off time for senior managers to be available, if needed.	Executives and senior managers should arrange their schedules to be on-site and available during the audit. Auditors do not like to be kept waiting and it could be detrimental if a member of your senior staff is not available to interview with the investigator.
☐ Make all documentation readily available.	Your documentation should already be prepared and organized, so this should be easy. However, you should ensure files and documents related to the Quality System are readily accessible to be provided to the investigator in a timely manner.
☐ Identify interviewees and subject matter experts (SMEs).	Alert department representatives and SMEs that they may be interviewed during the audit. Provide any coaching or mentoring for how to interact with the investigator.
☐ Review interview strategies and question styles.	Mock interviews should be part of your internal audit procedure but take the time to review interviewing techniques that will allow you to complete a successful inspection.

Summary and conclusion

This paper provides a brief discussion about what to expect before, during, and after an FDA QSR inspection or MDSAP QMS audit. However, there are many things that can and do occur during an inspection that cannot be fully detailed in this paper. The important thing to remember is that your organization must always be prepared for an inspection because the FDA can visit your facility at any time.

Utilize the internal audit program and corrective action system to ensure that deficiencies are identified internally, corrected and support compliance with the requirements. A well-prepared organization can face the challenge of audits with the goal of not receiving any FDA Form 483 observations or MDSAP findings, as applicable, and knowing they are providing safer, higher quality products to their customers.

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About the author

Linda Chatwin - United States, Lead Quality and Regulatory Affairs, has obtained approvals for a wide range of products, remains involved in changing requirements for medical devices worldwide. Linda has over 35 years of experience with medical products. Through years of watching regulations evolve and change, she knows how to navigate the global regulatory maze and bring products to market. Ms. Chatwin has obtained approvals for a wide range of products, remains involved in changing requirements for medical devices worldwide. She has navigated many FDA inspections, and other regulatory authority audits, and negotiated favorable outcomes with the FDA. Currently, she assists clients with regulatory issues and challenges, including implementation of UDI processes, mock audits, in-depth training on regulatory requirements, and consulting on quality system development and improvement and the MDSAP audit model. She has also conducted numerous trainings and gap assessments for the new MDR as well as SaMD requirements.

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