

**GxP Process Management Software**



**White Paper:**

*Ten Most Common Reasons for FDA  
483 Observations and Warning Letter  
Citations*

Most FDA violations involve one of the following:

- Not having procedures in a regulated area that conform to FDA regulations;
- Having procedures that conform to FDA regulations, but not following them; or
- Having procedures that conform to FDA regulations and following them, but not having adequate documentation to show that you're following them.

By sending an FDA-483 Obs. or Warning Letter, the FDA is communicating to a medical device company that its procedures are (or may be) inadequate in a specific regulated area for one of the above reasons.

At a recent Intermountain Biomedical Association workshop held in Lehi, Utah, Barbara Cassens, Director of the FDA's San Francisco District Office, identified ten specific FDA regulated areas in which medical device companies (as of July 30, 2007) most commonly receive FDA-483 Observations and Warning Letter citations.

### **1. Complaint Handling Procedures are Inadequate**

Section 21 CFR 820.198(a) states that a medical device manufacturer must maintain complaint files, as well as procedures for receiving, reviewing, and evaluating complaints. Such procedures must ensure that:

- All complaints are processed in a uniform and timely manner;
- Verbal complaints are documented upon receipt; and
- Complaints are evaluated to determine whether the complaint represents an event that must be reported to the FDA.

The regulation further requires that complaint files and procedures be contained “within a formally designated unit.”

### **2. Corrective and Preventive Action (CAPA) Procedures are Inadequate**

Under 21 CFR 820.100(a), manufacturers of medical devices must establish and maintain procedures for corrective and preventive actions, including procedures for:

- Analyzing processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems. Appropriate statistical methodology must be employed where necessary to detect recurring quality problems.
- Investigating the cause of nonconformities relating to products, processes, and the quality system.
- Identifying the action(s) needed to correct and prevent recurrence of nonconforming products or other quality issues.
- Verifying or validating a corrective and preventive action to ensure that it is effective and does not adversely affect the finished device.

- Implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems.
- Ensuring that information related to quality problems or a nonconforming product is disseminated to those directly responsible for assuring the quality of the product or preventing problems.
- Submitting relevant information on identified quality problems, as well as corrective and preventive actions, for management review.

### **3. Written Medical Device Reporting (MDR) Procedures are Inadequate**

Section 21 CFR 803.17 stipulates that manufacturers, user facilities, and importers of medical devices must develop, maintain, and implement written medical device reporting (MDR) procedures for internal systems. The procedures must provide:

- Timely and effective identification, communication, and evaluation of events that may be subject to MDR requirements;
- A standardized review process or procedure for determining when an event meets the criteria for MDR reporting; and
- Timely transmission of complete medical device reports to manufacturers or the FDA (or both, if required).

In addition, FDA regulation 21 CFR 803.17 requires manufacturers, user facilities, and importers of medical devices to establish documentation and recordkeeping requirements for:

- The information that was evaluated to determine whether an event was reportable;
- All medical device reports and information submitted to manufacturers and/or the FDA;
- Any information that was evaluated for the purpose of preparing the submission of annual reports; and
- Systems that ensure access to information for facilitating timely follow-up and inspection by the FDA.

### **4. Corrective and Preventive Actions are Inadequately Documented**

Under 21 CFR 820.100(b), manufacturers of medical devices must document all activities and results of activities related to corrective/ preventive action procedures. In other words, the FDA wants solid proof of a fully functional CAPA system that includes:

- A documented analysis of the sources of quality data (for example, incoming raw materials, manufacturing processes, inventory management, etc.);
- Documentation of investigations of the causes of nonconformities;
- Documentation of the actions needed to correct and prevent the recurrence of nonconforming products or other quality problems;

- Documentation of the procedures used to verify or validate corrective actions;
- Documentation of the procedures used in the implementation of corrective and preventative actions;
- Documentation that demonstrates that information about nonconforming products or quality problems is being properly disseminated to the responsible parties; and
- Documentation that demonstrates that information about nonconforming products (or quality problems) is being properly disseminated for management review.

## **5. Process Validation Procedures are Inadequate**

Under 21 CFR 820.75(a), where the results of a process cannot be fully verified by subsequent inspection and testing, the process must be validated with a high degree of assurance and approved according to established procedures. The validation activities and results, including the date and signature of the individual(s) approving the validation and, where appropriate, the major equipment validated, must be documented.

## **6. Quality Audits were not Adequately Conducted**

Section 21 CFR 820.22 states that quality audits must be conducted by individuals who do not have direct responsibility for the matters being audited, and corrective action(s), including a re-audit of deficient matters, must be taken when necessary. A report of the results of each quality audit, and re-audit(s) where taken, must be made and such reports must be reviewed by management having responsibility for the matters audited. The dates and results of quality audits and re-audits must be documented.

Hence, the sixth most common reason for getting an Obs. 483 or Warning Letter is because the FDA believes that a quality audit may not have been conducted properly, for one (or more) of the following reasons:

- The quality audit was not conducted by the proper individuals;
- Necessary corrective actions (including re-audits) were not taken;
- A report of the results of the quality audit (and any necessary re-audits) were not made according to FDA specifications; and/or
- The quality audit (or re-audit) report was not reviewed by management having responsibility for the matters audited.

## **7. Executive Management Failed to Ensure Quality at all Organizational Levels**

Under 21 CFR 820.20, management with executive responsibility must ensure an adequate and effective quality system at all levels of the organization.

- **Quality Policy:** Management with executive responsibility must establish its policy and objectives for, and commitment to, quality. Management with executive responsibility must also ensure that the quality policy is understood, implemented, and maintained at all levels of the organization.

- **Organization:** Each manufacturer must establish and maintain an adequate organizational structure to ensure that devices are designed and produced in accordance with the requirements listed below:
  - **Responsibility and authority:** Each manufacturer must establish the appropriate responsibility, authority, and interrelation of all personnel who manage, perform, and assess work affecting quality; in addition, each manufacturer must provide the independence and authority necessary to perform these tasks.
  - **Resources:** Each manufacturer must provide adequate resources, including the assignment of trained personnel, for the management and performance of work, and for assessment activities, including internal quality audits.
  - **Management representative:** Management with executive responsibility must appoint and document the appointment of a member of management who, irrespective of other responsibilities, must have established authority over and responsibility for (i) ensuring that quality system requirements are effectively established and effectively maintained in accordance with the stipulations defined in this section, and (ii) reporting on the performance of the quality system to management with executive responsibility for review.
- **Management review:** Management with executive responsibility must review the suitability and effectiveness of the quality system at defined intervals and with sufficient frequency according to established procedures to ensure that the quality system satisfies the requirements of this part and the manufacturer's established quality policy and objectives. The dates and results of quality system reviews must be documented.
- **Quality planning:** Each manufacturer must establish a quality plan which defines the quality practices, resources, and activities relevant to devices that are designed and manufactured. The manufacturer must establish how the requirements for quality will be met.
- **Quality system procedures:** Each manufacturer must establish quality system procedures and instructions. An outline of the structure of the documentation used in the quality system must be established where appropriate.

## 8. Procedures for Conducting Quality Audits are Inadequate

Under 21 CFR 820.22, manufacturers of medical devices must establish procedures for quality audits and conduct such audits to assure that their quality system is in compliance with their established quality system requirements, and to determine the effectiveness of their established quality system.

Hence, the eighth most common reason for getting an Obs. 483 or Warning Letter has to do with the manufacturer's procedures for conducting a quality audit. If the FDA believes that the procedures are inadequate, the reason may be because:

- The manufacturer doesn't have procedures for conducting quality audits;
- The manufacturer has procedures for conducting quality audits, but the procedures are not in compliance with the manufacturer's established quality system requirements; or

- The manufacturer has procedures that are in compliance with the manufacturer’s established quality system requirements, but the system requirements are not adequate for determining the effectiveness of the established quality system.

**9. Procedures for Controlling the Design Process are Inadequate**

Section 820.30(a) stipulates that each manufacturer of any class II or class III device, and the class I devices listed in below, must establish and maintain procedures for controlling the design of the device in order to ensure that specified design requirements are met.

**Class I devices that are subject to design controls include:**

- (i) Devices automated with computer software; and
- (ii) The devices listed in the following table:

Section	Device
868.6810	Catheter, Tracheobronchial Suction
878.4460	Glove, Surgeon’s
880.6760	Restraint, Protective
892.5650	System, Applicator, Radionuclide, Manual
892.5740	Source, Radionuclide Teletherapy

**10. Procedures for Design Changes are Inadequate or weren’t followed during the Design Change Validation/ Verification Process**

Section 820.30(i) stipulates that each manufacturer must establish and maintain procedures for identifying, documenting, validating (or, where appropriate, verifying), reviewing, and approving design changes before their implementation.

## The MasterControl™ Solution

MasterControl™ GxP process management software consists of configurable, easy-to-use, connected applications for automating, streamlining, and effectively managing document control, change control, training control, audits, corrective/preventive action (CAPA), customer complaints, and other documents- and forms-based quality and business processes under a single, web-based platform. Hundreds of companies use MasterControl to meet stringent FDA regulations and many others also use it to comply with ISO quality standards and Sarbanes-Oxley Act requirements.

### Here's how MasterControl helps avoid FDA 483 Obs. and Warning Letters:

Reason for Obs. 483 or Warning Letter	How MasterControl can Help
<p>#1 Complaint Handling Procedures are Inadequate</p> <p>21 CFR 820.198(a)</p>	<p>MasterControl Customer Complaints™ provides a simple, three-step process via a preconfigured, multi-page form for automating all tasks pertaining to customer complaints including:</p> <ul style="list-style-type: none"> <li>• Proper logging of complaints;</li> <li>• Capture of complete information from across the enterprise, regardless of who gets the complaint;</li> <li>• Data collection, notification, follow-up, and escalation;</li> <li>• Timely investigation; coordinated resolution; and</li> <li>• Shorter complaint (submission-to-resolution) lifecycle.</li> </ul> <p>Every step of the process is documented to ensure that all complaints, regardless of where they come from—e-mail, phone, fax, letters, corporate web site, sales reps, etc.—are properly logged, investigated, reported to the FDA (if warranted), and resolved in a timely manner.</p>
<p>#2 Corrective and Preventive Action (CAPA Procedures) are Inadequate</p> <p>21 CFR 820.100(a)</p>	<p>MasterControl CAPA™ automates all CAPA tasks, including routing, notification, follow-up, escalation, and approval of CAPAs and related documents. MasterControl CAPA is based on a team-oriented, problem-solving procedure involving an 8-step process (see description of 8-step process after this table).</p>

<p>#3 Written Medical Device Reporting (MDR) Procedures are Inadequate</p> <p>21 CFR 803.17</p>	<p>Medical device reporting (MDR) is the mechanism by which the FDA receives information about significant medical device adverse events. In its warning letters, FDA frequently cites a company's lack of a formal process for reviewing, evaluating, and investigating complaints, and reporting the serious cases to the agency via the MDR system. Thus, MDR deficiencies usually stem from improper complaint handling and reporting.</p> <p>As part of its customer complaints handling solution, MasterControl provides a pre-configured, multi-page electronic form that ensures the accurate capture of all relevant information from customer complaints. The solution includes the FDA's MedWatch 3500A form for mandatory reporting of adverse events to ensure that all required data are immediately collected and handed over to an adverse events specialist.</p>
<p>#4 Corrective and Preventive Action (CAPA) Procedures have not been Adequately Documented</p> <p>FDA regulation 21 CFR 820.100(b)</p>	<p>MasterControl CAPA tracks all routing information and data entered into the electronic CAPA form and stores this information in a centralized repository that makes search and retrieval easy during inspections and audits.</p>
<p>#5 Process Validation Procedures are Inadequate</p> <p>FDA regulation 21 CFR 820.75(a)</p>	<p>MasterControl supports process validation activities through its project and document management software. Designed to coordinate and track the rigorous validation testing, data analysis, and documentation requirements involved in developing a quality product for regulatory approval, MasterControl Projects™ connects the project plan to assigned tasks and provides automatic updates as soon as tasks are completed. Automating scheduling, task assignment, routing, tracking, escalation, and approval help ensure efficiency and quality, and greatly accelerate the validation process. Integrated document control capabilities make it easy to collaborate on, approve, and access protocols, reports, and test data.</p>

<p>#6 Quality Audits are not Adequately Conducted</p> <p>FDA regulation 21 CFR 820.22</p>	<p>To help ensure compliance, MasterControl Audit™ automates, streamlines, and effectively manages the audit process. The solution provides advanced tracking capabilities—from scheduling and planning through execution and completion—in addition to best practice forms for recording basic audit information and audit findings. MasterControl Audit automates the scheduling of all recurring audit-related activities and provides analytics and reporting capabilities for increased management visibility. (Please see Item #8 in this table for more information.)</p>
<p>#7 Executive Management Failed to Ensure Quality at all Organizational Levels</p> <p>FDA regulation 21 CFR 820.20</p>	<p>To help management ensure quality at all organizational levels, the MasterControl™ GxP Process Management Software suite provides configurable, easy-to-use, and connected solutions for automating, streamlining, and effectively managing document control, change control, training, audits, nonconformances, corrective/preventive action (CAPA), customer complaints, and other documents- and forms-based quality and business processes.</p> <p>MasterControl’s centralized document repository and web-based platform provide authorized users with access to up-to-date documents in the DHF, DHR, and DMR. In addition, system transparency and the system’s ability to generate customizable reports that provide the real-time status of the entire quality system keep members of the management team well informed, so that they can ensure quality at all organizational levels.</p>

<p>#8 Procedures for Conducting Quality Audits are Inadequate</p> <p>FDA regulation 21 CFR 820.22</p>	<p>A quality audit in a regulated company is the equivalent of a medical examination of a patient. It is a necessary procedure for evaluating a quality system’s general “health” and for “diagnosing” problems in order to correct them. MasterControl Audit™ automates all procedures pertaining to the audit process via two important best practice forms for collecting and tracking data:</p> <ul style="list-style-type: none"> <li>• <b>Audit Summary form</b>, which tracks basic information about an audit (type of audit, audit date, description, objective, and scope, audit area and lead auditor); this form also serves as a tool for gathering information, such as the regulation or procedure that is the basis for the audit, the audit agenda, audit team members, and checklists.</li> <li>• <b>Audit Finding form</b>, which tracks findings resulting from the audit and helps evaluate risk, based on the category and severity of risk and the likelihood of recurrence; this form also specifies whether a CAPA is required and provides proper closure by tracking verification of the process owner’s response to the finding.</li> </ul> <p>MasterControl Audit includes notification, follow-up, and escalation of overdue assignments to ensure that quality audits are completed on schedule.</p>
<p>#9 Procedures for Controlling the Design Process are Inadequate</p> <p>21 CFR 820.30(a)</p>	<p>MasterControl provides secure, centralized virtual vaults for the management of design control documents. Unreleased design documents can be locked to prevent multiple users from simultaneously changing the design. DIR, FMEA, test protocols and reports, as well as specifications and other documents created or reviewed during the product definition phase, reside in the “draft” vault while being worked on, and, when approved, automatically move to the “approved/ released” vault. This makes it easy for authorized users to locate the most recent version of design documents, and it prevents unauthorized design control documents from being accidentally released. Automatic archiving and cataloguing of “outdated” documents provides a GxP-compliant audit trail.</p>

<p>#10 Procedures for Design Changes are Inadequate or weren't followed during the Design Change Validation/ Verification Process</p> <p>21 CRF 820.30( i )</p>	<p>MasterControl Change Control™ helps ensure that procedures for design changes are both adequate and followed during the design change verification/validation process by providing a pre-configured, multi-page, best-practice, electronic form for collecting and tracking data throughout the entire change process.</p> <p>The form captures information such as description of change, justification, and impact. An initiator can use a single form for initiating multiple changes (for example, changes in a component and in ten products the component is used in). This assures the adequacy of the design change procedures by making sure that changes are immediately implemented in all affected components and devices.</p> <p>The form also incorporates priority level and prompts the user to make a risk assessment of the change (low, medium, or high). Any high-level change implies great impact on the product and is likely to require a regulatory filing. Customizable reports provide the real-time status not only of change control tasks but of the entire quality system.</p>
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<b>Eight Step CAPA Procedure</b>	
Step 1	Form an appropriate cross-functional team. The team should include a champion who has the resources and authority to implement the team's solution.
Step 2	Define the problem.
Step 3	Contain the problem. Protect the customer from the problem. This step can be omitted when 8D is used for a proactive improvement because there is no "problem" (like defective parts).
Step 4	Identify the root cause.
Step 5	Select a permanent correction.
Step 6	Implement the corrective action and verify its effectiveness.
Step 7	Make the change permanent (standardization). Also share the solution with similar operations. This is best practice deployment.
Step 8	Recognize the team's achievement.