FOOD AND DRUG
ADMINISTRATION

GUIDE TO INSPECTIONS OF QUALITY SYSTEMS

August 1999


Reports of Corrections and Removals
Medical Device Reporting
Medical Device Tracking
Corrective & Preventive Actions
Facility & Equipment Controls
Design Controls
MANAGEMENT
Material Controls
Production & Process Controls
Records/ Documents/ Change Controls
Sterilization Process Controls

Guide to Inspections of

Quality Systems

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Foreword

This document provides guidance to the FDA field staff on a new inspectional process that may be used to assess a medical device manufacturer's compliance with the Quality System Regulation and related regulations. The new inspectional process is known as the "Quality System Inspection Technique" or "QSIT". Field investigators may conduct an efficient and effective comprehensive inspection using this guidance material which will help them focus on key elements of a firm's quality system.

Note: This manual is reference material for investigators and other FDA personnel. The document does not bind FDA and does not confer any rights, privileges, benefits or immunities for or on any person(s).

Table of Contents

This reference is intended to be used in conjunction with the:

- ❒ Compliance Program Guidance Manual for Inspection of Medical Device Manufacturers (CP 7382.845).
- ❒ Investigations Operations Manual (IOM).
- ❒ Code of Federal Regulations, Title 21 (21 CFR) Part 820 Quality System Regulation; Part 803 Medical Device Reporting; Part 806 Medical Device Corrections and Removals; Part 821 Medical Device Tracking.
- ❒ Compliance Policy Guides (CPG) for devices (Sub Chapter 300).
- ❒ Guideline on General Principles of Process Validation, FDA, May 1987.

Other references include:

- ❒ The Federal Food, Drug, and Cosmetic Act; The Safe Medical Devices Act (SMDA) of 1990 and the Medical Device Amendments of 1992.
- ❒ Medical Device Quality Systems Manual: A Small Entity Compliance Guide.
- ❒ The FDA Worldwide Quality System Requirements Guidebook for Medical Devices.
- ❒ Other device specific guidance documents prepared by CDRH for the medical device industry.
- ❒ FDA Recognized Standards.

These additional guidances are posted to the CDRH Internet World Wide Web Home Page at http://www.fda.gov/cdrh.
See IOM Chapter 10, References, for additional information.

Performing Subsystem

Inspections

The Guide to Inspections of Quality Systems provides instructions for conducting medical device quality system/ GMP inspections. It is to be used in conjunction with the compliance program entitled Inspections of Medical Device Manufacturers (7382.845). The guide was prepared by the Food and Drug Administration (FDA) Office of Regulatory Affairs (ORA), and the Center for Devices and Radiological Health (CDRH). It provides guidance for inspecting medical device manufacturers against the Quality System Regulation (21 CFR Part 820) and related regulations.

This process for performing subsystem inspections is based on a "top-down" approach to inspecting. The subsystem approach is designed to provide you with the key objectives that can help determine a firm's state of compliance. The process was designed to account for the time constraints placed on field investigators when performing device quality system inspections. If you can focus your effort on key elements of a firm's quality system, you can efficiently and effectively evaluate that quality system.

When you begin an inspection by looking at one or more instances of quality problems, such as nonconforming device reports, and work your way back through the firm's quality system, you are doing a “bottom-up” inspection. This method has been helpful in zeroing in on specific problems, and evaluating the firm’s actions relating to those problems. However, with the “top-down” approach, we are looking at the firm’s “systems” for addressing quality before we actually look at specific quality problems. In the “top-down” approach, we “touch bottom” in each of the subsystems by sampling records, rather than working our way from records review backwards towards procedures.

The “top-down” approach begins each subsystem review with an evaluation of whether the firm has addressed the basic requirements in that subsystem by defining and documenting appropriate procedures. This is followed by an analysis of whether the firm has implemented the requirements of that subsystem.

The illustration provided inside the front cover of this book shows the seven subsystems, along with related satellite programs. Based on discussions between the device industry and the agency, we have chosen four major subsystems that are the basic foundation of a firm’s quality system. Those four major subsystems are Management Control; Corrective and Preventive Actions (CAPA) (with satellites Medical Device Reporting, Corrections and Removals, and Medical Device Tracking); Design Controls; and Production and Process Controls (P&PC) (with satellite Sterilization Process Controls). We have provided a

suggested technique for inspecting each of these four subsystems. In addition, following the chapter of the related subsystem we have provided suggested techniques for inspecting the satellite programs.

The satellite programs were included in the QSIT Inspection due to their correlation in the inspection process with the related subsystem. For instance, the CAPA subsystem is the logical "jumping-off" point to begin inspecting for Medical Device Reporting, Corrections and Removals, and Medical Device Tracking programs which relate to a firm's postmarket activities. In the case of the CAPA subsystem, if you are covering the satellite programs in your inspection, approximately half a day should be added to your subsystem inspection timeframe.

Rather than check every aspect of the firm's quality system, the subsystem approach focuses you on those elements that are most important in meeting the requirements of the quality system regulation and which are key quality indicators. Between 6-15 inspectional objectives are provided for the review of each subsystem. The review includes both a (broad) review of whether the firm has procedures in place, and appears to meet the requirements, and a closer (detailed) review of some records to verify that the requirements have been implemented in actual production, design and daily quality assurance situations.

One similarity between "top-down" and "bottom-up" inspectional approaches is record review. Both approaches involve review of raw data, or individual records. In the "top-down" approach, however, we are asking you to use

a sampling approach to the record review. With the "top-down" approach, you will sample records in many of the subsystems to verify whether or not the firm is in compliance. In other words, you are doing the raw data review as you did in the past, but in a more controlled manner. We have provided sampling tables to assist you in determining how many records you need to review, and what confidence you can have in the potential prevalence of the observed conditions.

One new feature in the "top-down" inspection technique is the use of *inspectional objectives* and *flow diagrams* to guide you during the inspection. We have provided inspectional objectives and flow diagrams that are useful in inspecting the four major subsystems. The flow diagrams provide a quick overview of how the inspection of each subsystem should occur.

In addition to the inspectional objectives and flow diagrams, we have provided a *narrative* description describing how to perform the inspection of each subsystem. The narrative description includes a discussion on how to achieve each inspectional objective and reflects the questions contained within the flow diagrams. You are not bound to follow each and every sentence in the narrative. Rather, you should inspect the subsystem with the narrative guidance in mind.

The Quality System Regulation (21 CFR 820.3(k)) defines "Establish" as "define, document (in writing or electronically), and implement". The Quality System Inspection Technique uses the "establish" approach in conduct-

ing the inspection. For each subsystem, you will first determine if the firm has defined and documented the requirements (CAPA, Design, etc.) by looking at procedures and policies, and then you will bore down into records, using the sampling tables, where appropriate, looking at raw data to determine if the firm is meeting their own procedures and policies, and if their program for executing the requirement is adequate.

The duration of inspection is related to the depth of the inspection. Keep in mind that the subsystem approach provides you with the key inspectional objectives that can help determine a firm's state of compliance. At the same time, the guidance was designed to accomplish a complete review of all four subsystems in approximately one week. While the length of your inspections will vary, using key inspectional objectives will help assure that you look at the most important elements of the firm's quality system during the inspection.

Most device firms are inspected more than once. By probing different subsystems, different devices or different processes each time, FDA will eventually have covered most of the firm's quality system. You are not expected to cover everything in the firm and in the narrative each time. You are expected to evaluate the firm's quality system, but also to do it in an efficient and focused manner. Thus, you should limit the depth of coverage when necessary to meet the time frame suggested. As a general rule of thumb, one day should be sufficient to cover each subsystem when using the "top-down" approach described within this document. In practice, you may find that the inspection of a certain

subsystem may take half a day, while another may take one and a half days. This situation would still reflect an overall one day per subsystem time frame.

By directing your attention to the major areas in a firm's quality system, you should be better able to determine if the firm's quality system is in control. Using the subsystem approach, you may find less opportunity to cite minor deviations from the quality system regulation than in the past. However, you will be citing more serious (systemic) deviations from the regulation.

PREANNOUNCED INSPECTIONS

The ORA Medical Device Industry Initiatives program encompasses preannounced medical device inspections, FDA 483 Annotation and Postinspectional Notification.

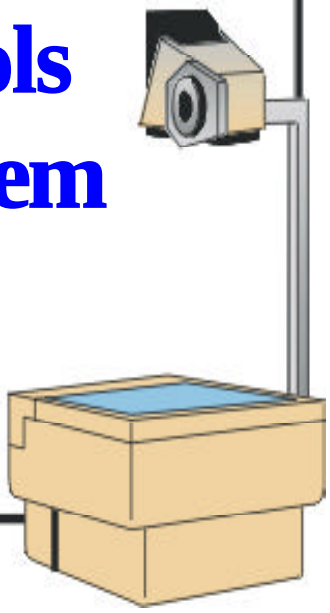
The instructions for *Preannouncement* (including the criteria to be used in determining when preannouncement is appropriate), *FDA 483 Annotation* and *Post-inspection Notification* were provided in an April 3, 1996, Federal Register Notice (Volume 61, Number 65). Refer to the Investigations Operations Manual (IOM) for further information.

When contacting the firm for the preannounced QSIT Inspection, the investigator should ask for a copy of the firm's Quality Policy and high level Quality System Procedures (including Management Review Procedures), Quality Manual, Quality Plan or equivalent documents to preview prior to the inspection. *The firm is not required to supply these documents.* The investigator should tell the firm that the preview of these procedural documents would facilitate the inspection. The documents would be returned at the time of the inspection. If you find deficiencies in these documents, you should request copies of the original documents after you initiate the inspection.

GETTING STARTED

It is essential that the firm establishes and maintains a quality system that is appropriate for the specific medical device being manufactured and meets the requirements of the Quality System Regulation. The Management Representative has the responsibility to ensure that the requirements of the Quality System Regulation have been effectively established and maintained. Prior to your review of any subsystem, interview the Management Representative (or designee). The objective of this interview is to obtain an overall view of the subsystem as well as a feel for management's knowledge and understanding of the subsystem. An important linkage for this activity is Management Controls (820.20 Management Responsibility).

Management Controls Subsystem



Management Controls

Inspectional Objectives

1. Verify that a quality policy, management review and quality audit procedures, quality plan, and quality system procedures and instructions have been defined and documented.

2. Verify that a quality policy and objectives have been implemented.

3. Review the firm's established organizational structure to confirm that it includes provisions for responsibilities, authorities and necessary resources.

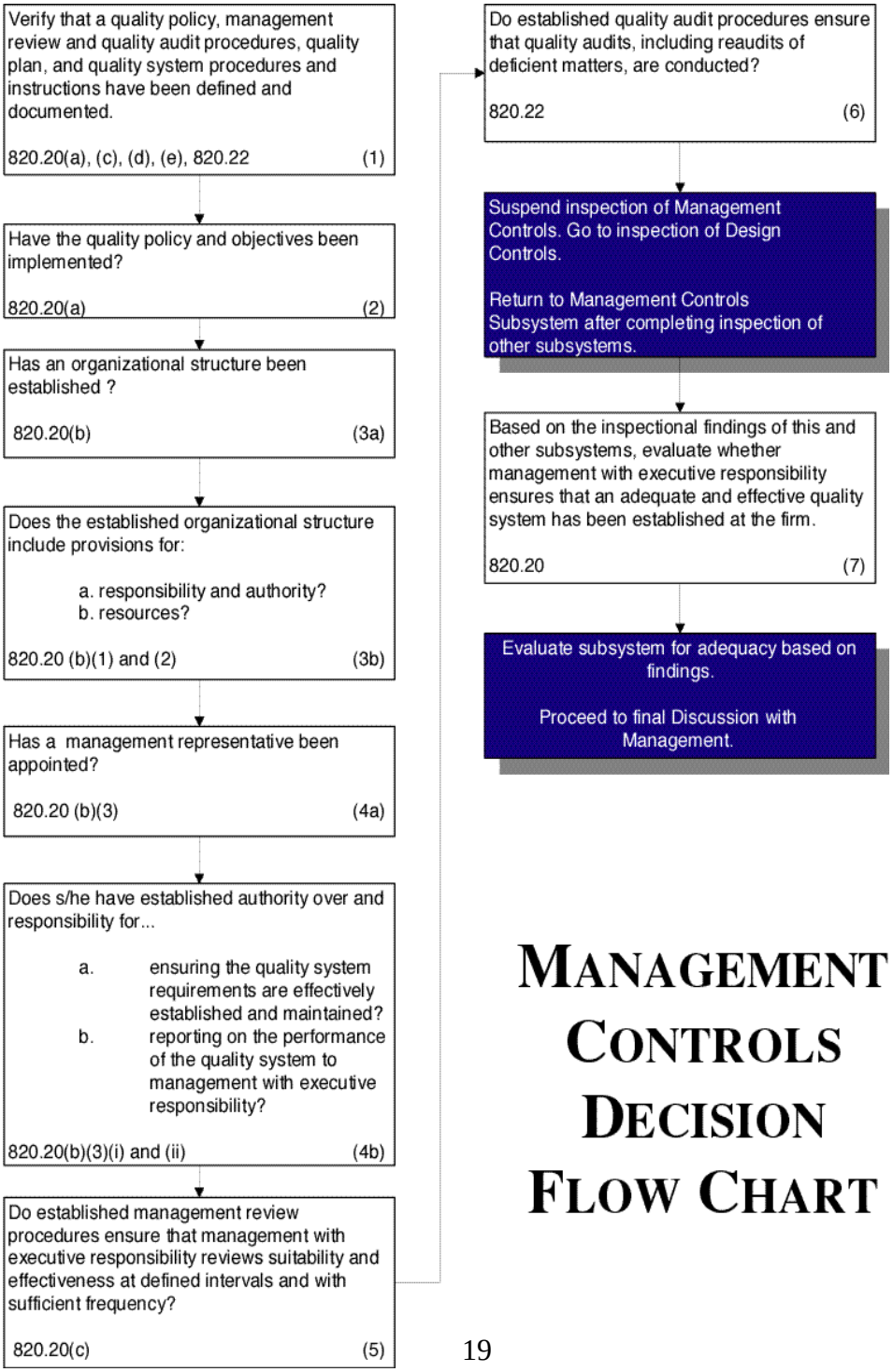
4. Confirm that a management representative has been appointed. Evaluate the purview of the management representative.

5. Verify that management reviews, including a review of the suitability and effectiveness of the quality system, are being conducted.

6. Verify that quality audits, including re-audits of deficient matters, of the quality system are being conducted.

At the conclusion of the inspection....

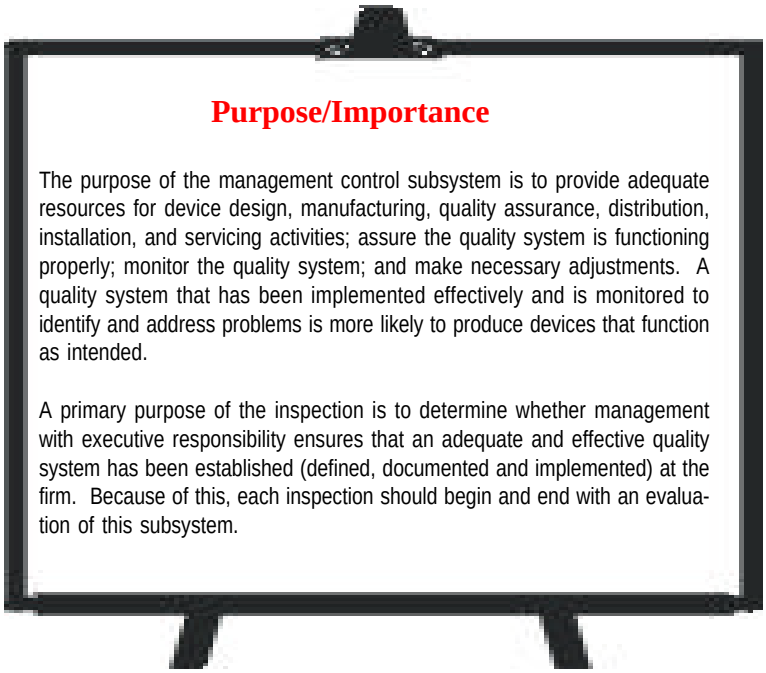
7. Evaluate whether management with executive responsibility ensures that an adequate and effective quality system has been established and maintained.



MANAGEMENT CONTROLS DECISION FLOW CHART

Management Controls

Narrative



Purpose/Importance

The purpose of the management control subsystem is to provide adequate resources for device design, manufacturing, quality assurance, distribution, installation, and servicing activities; assure the quality system is functioning properly; monitor the quality system; and make necessary adjustments. A quality system that has been implemented effectively and is monitored to identify and address problems is more likely to produce devices that function as intended.

A primary purpose of the inspection is to determine whether management with executive responsibility ensures that an adequate and effective quality system has been established (defined, documented and implemented) at the firm. Because of this, each inspection should begin and end with an evaluation of this subsystem.

1. Verify that a quality policy, management review and quality audit procedures, quality plan, and quality system procedures and instructions have been defined and documented.

Prior to the start of the inspection, preferably at the time you make the preannouncement of the inspection (if preannounced), you should ask the firm to send you their overall (or top level) quality system policies, objectives, and procedures. This should include their management review procedures, quality policy, and quality plan. If not received prior to the start of the inspection, you will need to review these documents at the start of your inspection.

Quality Policy and Objectives

The firm must have a written quality policy. The definition of quality policy is provided in the Quality System Regulation. It means the overall intentions and directions of an organization with respect to quality. The firm is responsible for establishing a clear quality policy with achievable objectives then translating the objectives into actual methods and procedures. Management with executive responsibility (i.e. has the authority to establish and make changes to the company quality policy) must assure the policy and objectives are understood and implemented at all levels of their organization. The policy does not need to be extensive. Personnel are not required to be able to recite the policy but they should be familiar with it and know where to obtain it.

Management Review and Quality Audit Procedures

Management reviews and quality audits are a foundation of a good quality system. Assure that the manufacturer has written procedures for conducting management reviews and quality audits and there are defined intervals for when they should occur. The firm's quality audits should examine the quality system activities to demonstrate that the procedures are appropriate to achieve quality system objectives, and the procedures have been implemented. A successful implementation of the firm's procedures should result in the firm achieving its quality policy and associated objectives. Whether the quality policy and objectives are "good" may become evident as the other subsystems are reviewed during the inspection.

Quality Plans

The firm must have a written quality plan that defines the quality practices, resources and activities relevant to the devices that are being designed and manufactured at that facility. The manufacturer needs to have written procedures that describe how they intend to meet their quality requirements.

For firms that manufacture devices as well as other products, there must be a quality plan that is specifically relevant to devices. Much of what is required to be part of the plan may be found in the firm's quality system documentation, such as, the Quality Manual, Device Master Record(s), production procedures, etc. Therefore, the plan itself may be a roadmap of the firm's quality system. The plan in this case would need to include reference to applicable quality system documents and how those documents apply to the device(s) that is the subject of the plan.

Quality plans may be specific to one device or be generic to all devices manufactured at the firm. Quality plans can also be specific to processes or overall systems.

Quality System Procedures and Instructions

All manufacturers of medical devices are required to establish and implement a quality system tailored to the device manufactured. Each manufacturer must prepare and implement all activities, including, but not necessarily limited to the applicable requirements of the Quality System Regulation, that are necessary to assure the finished device, the design process, the manufacturing process, and all related activities conform to approved specifications.

The term "quality system" as specified in the Quality System Regulation encompasses all activities previously referred to as "quality assurance" which were necessary to

assure the finished device meets its predetermined design specifications. This includes assuring manufacturing processes are controlled and adequate for their intended use, documentation is controlled and maintained, equipment is calibrated, inspected, tested, etc. Some manufacturers may use the terms "quality control" or "GMP Control" or "quality assurance" instead of quality system. It doesn't matter what term is used as long as the quality system concept is understood and implemented.

Written quality system procedures and instructions are required. Any FDA 483 observation regarding Quality System procedures must be specific and point out the controls that are missing or believed inadequate.

2. Verify that a quality policy and objectives have been implemented.

One way to determine whether personnel are familiar with the quality policy is to ask employees directly. This should not be done when the employee is engaged in the actual performance of his/her duties, but could be done when he/she is at break or when he/she has finished a task and before he/she begins his/her next task.

You can also look to see how management has made the policy available. For example: Is it in their Quality Manual or another part of their written procedures? Is it posted at points throughout the building? It doesn't matter how they made the policy known, only that personnel know that there is a policy and where they can read the policy for themselves.

A review of employee training records to show they have been trained in the firm's quality policy and objectives can also be done. In particular, this should be done for those employees involved in key operations.

3. Review the firm's established organizational structure to confirm that it includes provisions for responsibilities, authorities and necessary resources.

The firm's organizational structure must be adequate to ensure devices are designed and manufactured in accordance with the Quality System Regulation. The organizational structure should ensure the technical, administrative, and human factors functions affecting the quality of a device are controlled. These functions may involve hardware, software, processed materials or services. All such control should be towards the reduction, elimination, or ideally, the prevention of quality nonconformities.

To determine what the firm's organizational structure is, start by asking the authority and responsibility questions that are the start of every FDA inspection. Review the firm's organizational charts.

The firm's procedures should describe the functional areas or people responsible for performing certain tasks governed by their quality system. They should also include provisions for resources and designating a management representative.

Determine whether personnel involved in managing, performing or assessing work affecting quality have the necessary independence and authority to perform those tasks. Organizational freedom or independence does not necessarily require a stand-alone group. However, the responsibility, authority and independence should be sufficient to attain the firm's stated quality objectives.

Adequate resources must be available for the quality system to assure the firm's stated quality objectives can be achieved. Resources include money, supplies, personnel, etc. One approach to confirm that adequate resources are available is to ask the management representative how resources are obtained and allocated.

4. Confirm that a management representative has been appointed. Evaluate the purview of the management representative.

The firm must appoint a management representative who is responsible for ensuring the quality system is effectively established and maintained, and who will report on its performance to management with executive responsibility for review. *The appointment must be documented.*

To determine whether there is in fact a documented management representative, review the firm's organizational chart(s) or their Quality Manual.

Determine whether the appointed management representative actually has the purported responsibility and authority granted to him/her by the firm's procedures or organizational structure. Ways of reaching this determination include: Whether he/she has sign-off authority for changes to documents, processes, or product designs; whether the people conducting quality audits report or provide him/her with their results; and noting how he/she interacts with corrective and preventive actions, relative design control issues, complaints, MDRs, in-process or finished product failures, etc. In other words, his /her responsibility and authority should be apparent through the review of the other subsystems.

Verify that the management representative is reporting back to the management with executive responsibility on the performance of the quality system. These reports should either be the subject of the management reviews or at least provide the framework for those reviews.

NOTE: The agency's policy relative to the review of quality audit results is stated in CPG 7151.02 (CPG Manual subchapter 130.300). This policy prohibits FDA access to a firm's audit results. Under the Quality System Regulation, this prohibition extends to reviews of supplier audit reports and management reviews. However, the procedures and documents that show conformance with 21 CFR 820.50, Purchasing Controls, and 21 CFR 820.20(3)(c), Management Reviews, and 21 CFR 920.22 Quality Audit, are subject to FDA inspection.

5. Verify that management reviews, including a review of the suitability and effectiveness of the quality system, are being conducted.

Management reviews must measure the firm's quality system against the Quality System Regulation and the firm's own stated quality objectives as defined in their quality policy. Management reviews must be documented. There must be written procedures for conducting management reviews. These procedures can be inspected and the firm must certify in writing, if requested, that the firm has complied with this Quality System Regulation requirement.

Review the firm's management review schedule to confirm management reviews are being conducted with sufficient frequency. Management reviews should be frequent enough to keep them informed of ongoing quality issues and problems. During your review of the CAPA subsystem, if you find that there are quality issues that do not seem to be known to executive-level management, then the reviews may not be occurring with sufficient frequency.

The dates and results of management reviews must be documented to show dates conducted and whether management with executive responsibility attended the reviews. It is not permissible as explained above for an FDA Investigator to review the firm's actual management review documentation. However, the firm should be able to show you how the reviews are to be documented. Management review procedures or instructions should include a requirement that the results of the reviews be documented and dated.

6. Verify that quality audits, including re-audits of deficient matters, of the quality system are being conducted.

Review the firm's quality audit schedules to assure quality audits are being conducted with sufficient frequency. It is recommended that the time between quality audits not exceed a 12-month period. More frequent audits may be recommended if the firm has a serious Quality System Regulation problem.

Quality audits should consist of a formal, planned check of all elements in the quality system. They are **NOT** product audits. Quality audits must be conducted using adequate detailed written procedures by appropriately trained individuals. If conducted properly, a quality audit can detect system defects and, through isolation of unsatisfactory trends and correction of factors that cause defective products, prevent the production of unsafe or nonconforming devices. *Without an effective quality audit function the quality system is incomplete and there is no assurance the manufacturer is consistently in a state-of-control.*

Evidence of inadequate auditing may exist without gaining access to the written quality audit reports. This evidence may be obtained by relating the audit program to deficiencies observed in other subsystems. If significant quality system problems have existed both before and after the firm's last self-audit, then you should critically review the written audit procedures. The audit procedures should cover each quality system, and should be specific enough to enable the person conducting the audit to perform an adequate audit. The auditors must be adequately trained. If it is necessary and possible to interview an auditor, ask how the audits are performed; what documents are examined; how long audits take; etc.

Audits should be conducted by individuals not having direct responsibility for matters being audited. One person and other very small firms must generally establish independence, even if it means hiring outside auditors, because the failure to have an independent auditor could result in an ineffective audit. *If there are significant FDA 483 observations, and independent audits are being performed, but deficiencies are apparently not being identified by the auditor, then an FDA 483 should contain an observation indicating a lack of adequate audits.*

Determine whether corrective action by upper management is being taken. Auditors may be asked if they observed any of the ongoing Quality System Regulation deficiencies during their prior audits (ongoing Quality System Regulation deficiencies may also be identified by reviewing prior FDA 483's). If the answer is yes, check the written audit schedule, if available, to determine if a follow up audit is scheduled for the deficient areas. Check the written audit procedure for instructions for review of audits by upper management . For example, do the procedures require quality audit results to be included in the management reviews? Verify that the procedures contain provisions for the re-audit of deficient areas if necessary. A failure to implement follow-up corrective actions, including re-audits of deficient matters may be listed as a Quality System Regulation deficiency on the FDA 483.

NOTE: Re-audits of deficient matters are not always required, but where one is indicated, it must be conducted. The reaudit report should verify the recommended corrective action(s) was implemented and effective.

7. Evaluate whether management with executive responsibility ensures that an adequate and effective quality system has been established and maintained.

At this point in QSIT, you stop your review of the management system. You continue your inspection by evaluating the other subsystems. While you evaluate the other subsystems, keep thinking about what you are finding and whether it indicates that management is appropriately carrying out responsibilities for providing adequate resources and overseeing the quality system to detect problems and address them.

From your review of the other subsystems, you have a better idea on whether the management representative has the appropriate authority and responsibility, whether the organizational structure is adequate, whether the quality audits and management reviews are sufficient, whether the quality policy has really been implemented, and whether the training being provided is sufficient.

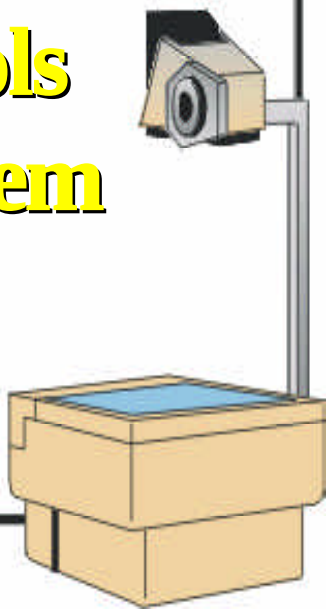
You need to take the time after reviewing the other subsystems, to evaluate the inspectional findings of the management and other subsystems. You need to determine whether the management representative and management with executive responsibility are ensuring the adequacy and effectiveness of the quality system and whether that system has been fully implemented at this firm.

If you found major nonconformances (as defined in the Compliance Program, Part V) in your review of the management or other subsystems that indicate management with executive responsibility is not ensuring the establishment and maintenance of an adequate quality system, you may cite this deficiency on your FDA 483. This cite should not

be used routinely, but should be used in those situations where major portions of a quality system have not been established and maintained or whenever there is a total lack of a quality system.

When you have made that determination and have completed your FDA 483, or decided no FDA 483 is needed, you may proceed to your final discussion with Management, or the official closeout meeting with the firm.

Design Controls Subsystem



Design Controls

Inspectional Objectives

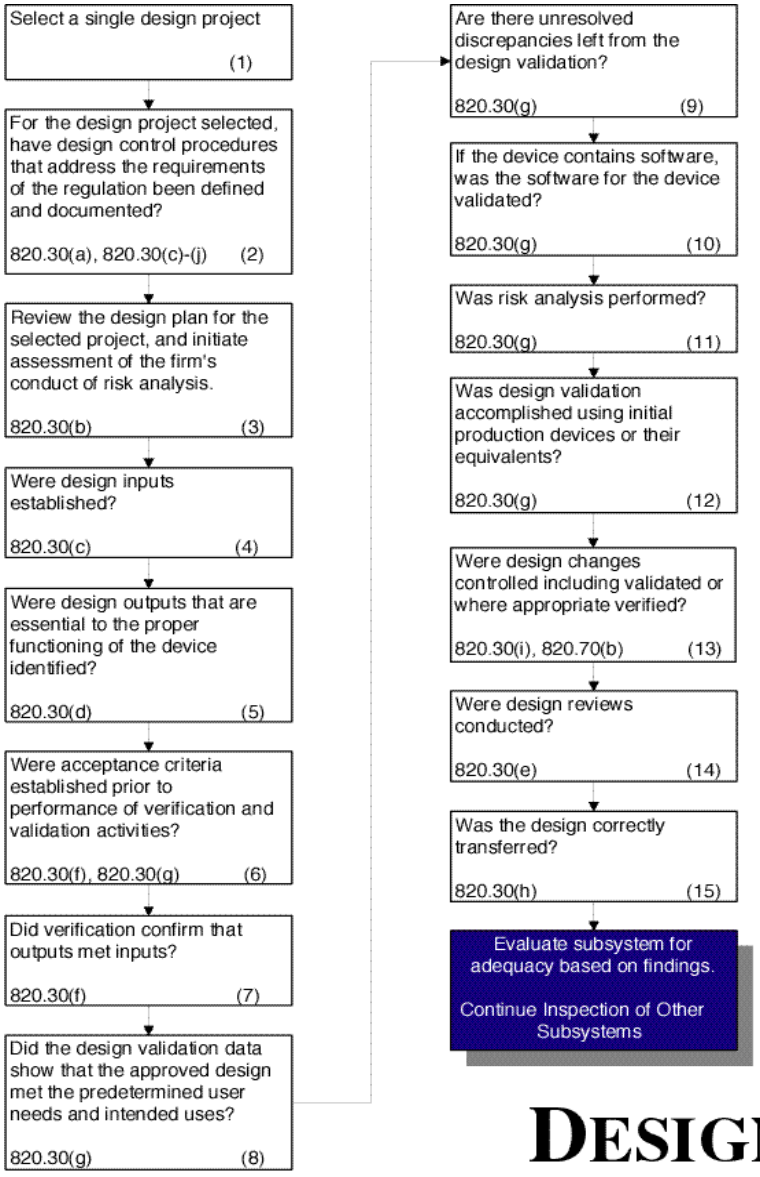
1. Select a single design project.

Note: If the project selected involves a device that contains software, consider reviewing the software's validation while proceeding through the assessment of the firm's design control system.

2. For the design project selected, verify that design control procedures that address the requirements of Section 820.30 of the regulation have been defined and documented.
3. Review the design plan for the selected project to understand the layout of the design and development activities including assigned responsibilities and interfaces.

Note: Evaluate the firm's conduct of risk analysis while proceeding through the assessment of the firm's Design Control system.

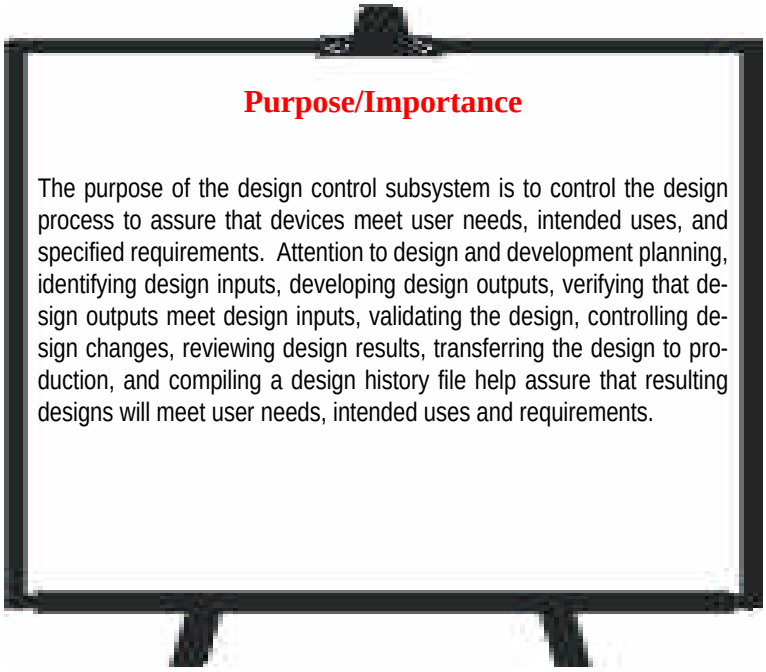
4. Confirm that design inputs were established.
5. Verify that the design outputs that are essential for the proper functioning of the device were identified.
6. Confirm that acceptance criteria were established prior to the performance of verification and validation activities.
7. Determine if design verification confirmed that design outputs met the design input requirements.
8. Confirm that design validation data show that the approved design met the predetermined user needs and intended uses.
9. Confirm that the completed design validation did not leave any unresolved discrepancies.
10. If the device contains software, confirm that the software was validated.
11. Confirm that risk analysis was performed.
12. Determine if design validation was accomplished using initial production devices or their equivalents.
13. Confirm that changes were controlled including validation or where appropriate verification.
14. Determine if design reviews were conducted.
15. Determine if the design was correctly transferred.



DESIGN CONTROLS DECISION FLOW CHART

Design Controls

Narrative



☑ **1. Select a single design project.**

Note: If the project selected involves a device that contains software, consider reviewing the software's validation while proceeding through the assessment of the firm's design control system.

The design control requirements of Section 820.30 of the regulation apply to the design of Class II and III medical devices, and a select group of Class I devices. The regulation is very flexible in the area of design controls. The type of design control system and the precise details of implementation are left for each firm to decide based on the complexity and risks associated with their devices.

If design control requirements are applicable to the operations of the firm, *select a design project.* Unless the inspection assignment directs the inspection of a particular design project, select a project that provides the best challenge to the firm's design control system. This project will be used to evaluate the process, the methods, and the procedures that the firm has established to implement the requirements for design controls.

Do not inspect a device under design control requirements to determine whether the design was appropriate or safe and effective. This is precluded under Section 520(f)(1)(A) of the Act. However, if based on information obtained during an evaluation of the firm's design controls, it appears that the device is unsafe or ineffective, then report those findings in the EIR.

The requirement for software validation is included in Section 820.30(g) Design Validation. However, if the project selected involves a device that contains software, consider reviewing the software's validation while proceeding through the assessment of the firm's design control system.

If the firm has not completed a design project, has no ongoing or planned design projects, and has not made a design change, proceed to the narrative discussion under Objective 2 and limit your review of design controls to those instructions.

2. For the design project selected, verify that design control procedures that address the requirements of Section 820.30 of the regulation have been defined and documented.

Firms, including small firms and those who design simple devices, who are subject to Section 820.30 of the regulation, are required to define, and document, either in writing or electronically, procedures which address the requirements of the regulation. These procedures serve to set the structure for the firm's design control system.

However, if the firm has not completed any design projects, has no ongoing or planned design projects, and has not made a design change, it is only required to maintain a defined and documented design change procedure.

Review the firm's design control procedures and verify that they address the specific requirements of the regulation. As examples, determine if the design input procedures include a mechanism for addressing incomplete, ambiguous, or conflicting requirements; the design output procedures ensure that those design outputs that are essential for the proper functioning of the device are identified; and the design review procedure ensures that each design review includes an individual(s) who does not have direct responsibility for the design stage being reviewed.

In order to determine if the firm's design control procedures have been implemented, use the selected design project to exercise the firm's procedures and accomplish the following objectives.

3. Review the design plan for the selected project to understand the layout of the design and development activities including assigned responsibilities and interfaces.

Note: Evaluate the firm's conduct of risk analysis while proceeding through the assessment of the firm's Design Control system.

The firm's development of concepts and the conduct of feasibility studies are not subject to the design control requirements of the regulation. However, once the firm decides that a design will be developed, a design plan must be established. A firm will determine when it will begin to apply design controls. However, design controls must be applied no later than the time the firm approves its first set of inputs.

Utilize the firm's design plan as a road map for the selected design project. Plans include major design tasks, project milestones, or key decision points. It is not necessary for plans to show starting or completion dates for activities covered by the plan. Plans may vary depending on the complexity of the project and the degree of risk associated with the device. Plans may take the form of a simple flow chart for less complex projects or may be expressed as Program Evaluation and Review Technique (PERT) or Gantt charts for larger projects. However, plans must define responsibility for implementation of the design and development activities and identify and describe interfaces with different groups or activities.

While the requirement for the conduct of risk analysis appears in Section 820.30(g) Design Validation, a firm should not wait until they are performing design validation to begin risk analysis. Risk analysis should be addressed in the design plan and risk should be considered throughout the design process. Risk analysis must be completed in design validation.

When conducting risk analysis, firms are expected to identify possible hazards associated with the design in both normal and fault conditions. The risks associated with those hazards, including those resulting from user error, should then be calculated in both normal and fault conditions. If any risk is deemed unacceptable, it should be reduced to acceptable levels by the appropriate means, for example by redesign or warnings. An important part of risk analysis is ensuring that changes made to eliminate or minimize hazards do not introduce new hazards.

Common tools used by firms to conduct risk analyses include Fault Tree Analysis (FTA), and Failure Modes and Effects Analysis (FMEA).

4. Confirm that design inputs were established.

Inputs are the requirements of a device. They must be documented. Review the sources used to develop inputs. Determine that relevant aspects were covered. Examples of relevant aspects include: intended use, performance characteristics, risk, biocompatibility, compatibility with the environment of intended use including electromagnetic compatibility, human factors, voluntary standards, and sterility.

5. Verify that the design outputs that are essential for the proper functioning of the device were identified.

Design outputs are the work products or deliverables of a design stage. Examples include, diagrams, drawings, specifications and procedures. The outputs from one stage may become inputs to the next stage. The total finished design output consists of the device, its packaging and labeling, and the device master record. Important linkages to consider are Sections 820.80 Receiving, in-process, and finished device acceptance, 820.120 Device labeling, and 820.130 Device packaging.

Design projects can produce a large volume of records. Not all of the records generated during the project are design outputs and as such do not need to be retained in the design history file. Only approved outputs need to be retained.

Outputs must be comprehensive enough to characterize the device design to allow for verification and validation. Also, design outputs which are essential for the proper functioning of the device must be identified. Typically a risk analysis tool such as FTA or FMEA is used to determine essential outputs. For the selected project, verify that essential outputs have been identified. In addition, review the firm's process for determining how the essential outputs were identified and determine if it was done in accordance with their design output procedures. Important linkages to consider are Sections 820.50 Purchasing controls, and 820.100 Corrective and preventive action.

6. Confirm that acceptance criteria were established prior to the performance of verification and validation activities.

Verification and validation activities should be predictive rather then empiric. Acceptance criteria must be stated up front. Review the documentation associated with a sample of verification activities and a sample of validation activities as determined using the Sampling Tables. If possible, select activities that are associated with outputs identified as essential to the proper functioning of the device. Confirm that acceptance criteria were established prior to performance of the verification or validation activity.

7. Determine if design verification confirmed that design outputs met the design input requirements.

Design verification activities are performed to provide objective evidence that design output meets the design input requirements. Verification activities include tests, inspections, analyses, measurements, or demonstrations. Activities should be explicit and thorough in their execution. It is the firm's responsibility to select and apply appropriate verification techniques. Complex designs can require more and different types of verification activities than simple designs. Any approach selected by the firm, as long as it establishes conformance of the output to the input, is an acceptable means of verifying the design with respect to that requirement.

Review the documentation of the verification activities associated with a sample of inputs and outputs as determined using the Sampling Tables. If possible, select activities that are associated with outputs identified as essential to the proper functioning of the device. Confirm that design outputs met design input requirements.

8. Confirm that design validation data show that the approved design met the predetermined user needs and intended uses.

Design validation is performed to provide objective evidence that device specifications (outputs) conform with user needs and intended use(s). Design validation must be completed before commercial distribution of the device.

Design validation involves the performance of clinical evaluations and includes testing under actual or simulated use conditions. Clinical evaluations can include clinical investigations or clinical trials, but they may only involve other activities. These may include evaluations in clinical or non-

clinical settings, provision of historical evidence that similar designs are clinically safe, or a review of scientific literature. Validation activities must address the needs of all relevant parties (i.e. patient, health care worker, etc.) and be performed for each intended use. Validation activities should address the design outputs of labeling and packaging. These outputs may have human factor implications, and may adversely affect the device and its use.

If possible, review the evaluations (clinical or other activities) performed to assist in validating the device design.

9. Confirm that the completed design validation did not leave any unresolved discrepancies.

Design validation may detect discrepancies between the device specifications (outputs) and the needs of the user or intended use(s) of the device. All discrepancies must be addressed and resolved by the firm. This can be accomplished through a change in design output or a change in user need or intended use.

10. If the device contains software, confirm that the software was validated.

As previously noted, design validation includes the requirement for software validation. If the selected device is software controlled its software must be validated.

11. Confirm that risk analysis was performed.

As previously noted, risk analysis must be completed in design validation.

12. Determine if design validation was accomplished using initial production devices or their equivalents.

Initial production units, lots, or batches, or their equivalents are to be used in design validation. Confirm that such production devices or their equivalents were used by reviewing the design validation documentation. If production devices were not used, the firm must demonstrate equivalency to production devices. When the so called "equivalent" devices are used in design validation the manufacturer must document in detail how the device was manufactured, and how the manufacturing is similar and possibly different from initial production. Where there are differences, the manufacturer must justify why design validation results are valid for production units, lots or batches. The regulation is flexible and it does allow for the use of equivalent devices, but the burden is on the manufacturer to document that the units were indeed equivalent.

Process validation may be conducted concurrently with design validation. Production devices used in design validation may have been manufactured in a production run during process validation.

13. Confirm that changes were controlled including validation or where appropriate verification.

Change control is not a new requirement. The 1978 GMP regulation Section 820.100(a)(2) required approval of changes made to specifications after final design transfer (post-production changes). The Quality System regulation clarified and relocated the requirement into Section 820.30(i). It expanded the requirement to include changes made during the design process (pre-production changes).

The documentation and control of design changes begin when the initial design inputs are approved and continues

for the life of the product. Examples of the application of change control include: changes made to approved inputs or outputs such as to correct design deficiencies identified in the verification and validation activities; labeling changes; changes which enhance the device's capabilities or the capabilities of the process; and changes resulting from customer complaints.

Product development is inherently an evolutionary process. While change is a healthy and necessary part of product development, quality can be ensured only if change is controlled and documented in the development process, as well as in the production process.

The degree of design change control is dependent on the significance of the change and the risk presented by the device. Manufacturers may use their routine post-production change control procedure for pre-production design changes. However, most post-production change control procedures may be too restrictive and stifle the development process. Firms may use a separate and less stringent change control procedure for pre-production design changes.

Post-production design changes require the firm to loop back into the design controls of Section 820.30 of the regulation. This does not mean that post-production changes have to go back to the R&D Department for processing. This track is dependent on what the firm specifies in their change procedure. It is acceptable for the manufacturing department to process the entire design change and to implement the controls of Section 820.30.

The design change control section is linked to and is redundant with Section 820.70(b) Production and process changes of the regulation.

All design changes must be verified. Design changes must also be validated unless the performance of only verification can be justified and documented by the firm. Where a design change cannot be verified by subsequent inspection and test, it must be validated. For example, a change in the intended use of the device will require validation. However, if a firm was making a design change in the material used in the device, then verification through analysis may only be required. The burden is on the firm to justify and document why verification only is appropriate in lieu of validation.

Review a pre-production and a post-production design change.

14. Determine if design reviews were conducted.

Formal design reviews are planned and typically conducted at the end of each design stage or phase, or after completion of project milestones. The number of reviews is dependent on the complexity of the design. A single review may be appropriate at the conclusion of the design project for a simple design or a minor change to an existing product. Multiple reviews are typically conducted for projects involving subsystems or complex designs.

Design reviews should provide feedback to designers on existing or emerging problems, assess the progress of the design, and confirm the design is ready to move to the next phase of development. Reviews should focus on the ability to produce the design and whether the design meets the input requirements.

The design review process should account for risk analysis and change control where relevant.

Full convened meetings with an agenda, minutes, etc. need not take place for all design reviews. Meetings may not be necessary for reviews involving simple designs or minor changes. In these cases desk reviews and sign-offs by the various organizational components including an individual not having direct responsibility for the design stage being reviewed may be appropriate. However, such reviews must still be documented and covered by defined and documented procedures.

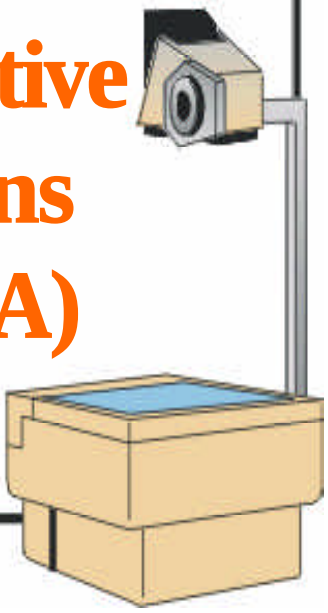
Review the records of one design review and confirm that the review included an individual without direct responsibility for the design stage being reviewed. Also, confirm that outstanding action items are being resolved or have been resolved.

15. Determine if the design was correctly transferred.

The transfer process must be a part of the design plan. It is not uncommon for the design to be transferred in phases. Production specifications typically consist of written documents such as assembly drawings, inspection and test specifications, and manufacturing instructions. However, they can also consist of electronic records, training materials such as video tapes or pictures, and manufacturing jigs and molds.

Review how the design was transferred into production specifications. Review the device master record. Sample the significant elements of the device master record using the Sampling Tables and compare these with the approved design outputs. These elements may be chosen based on the firm's previously identified essential requirements and risk analysis.

Corrective and Preventive Actions (CAPA)



Corrective and Preventive Actions (CAPA)

Inspectional Objectives

1. Verify that CAPA system procedure(s) that address the requirements of the quality system regulation have been defined and documented.

2. Determine if appropriate sources of product and quality problems have been identified. Confirm that data from these sources are analyzed to identify existing product and quality problems that may require corrective action.

3. Determine if sources of product and quality information that may show unfavorable trends have been identified. Confirm that data from these sources are analyzed to identify potential product and quality problems that may require preventive action.

4. Challenge the quality data information system. Verify that the data received by the CAPA system are complete, accurate and timely.

5. Verify that appropriate statistical methods are employed (where necessary) to detect recurring quality problems. Determine if results of analyses are compared across different data sources to identify and develop the extent of product and quality problems.

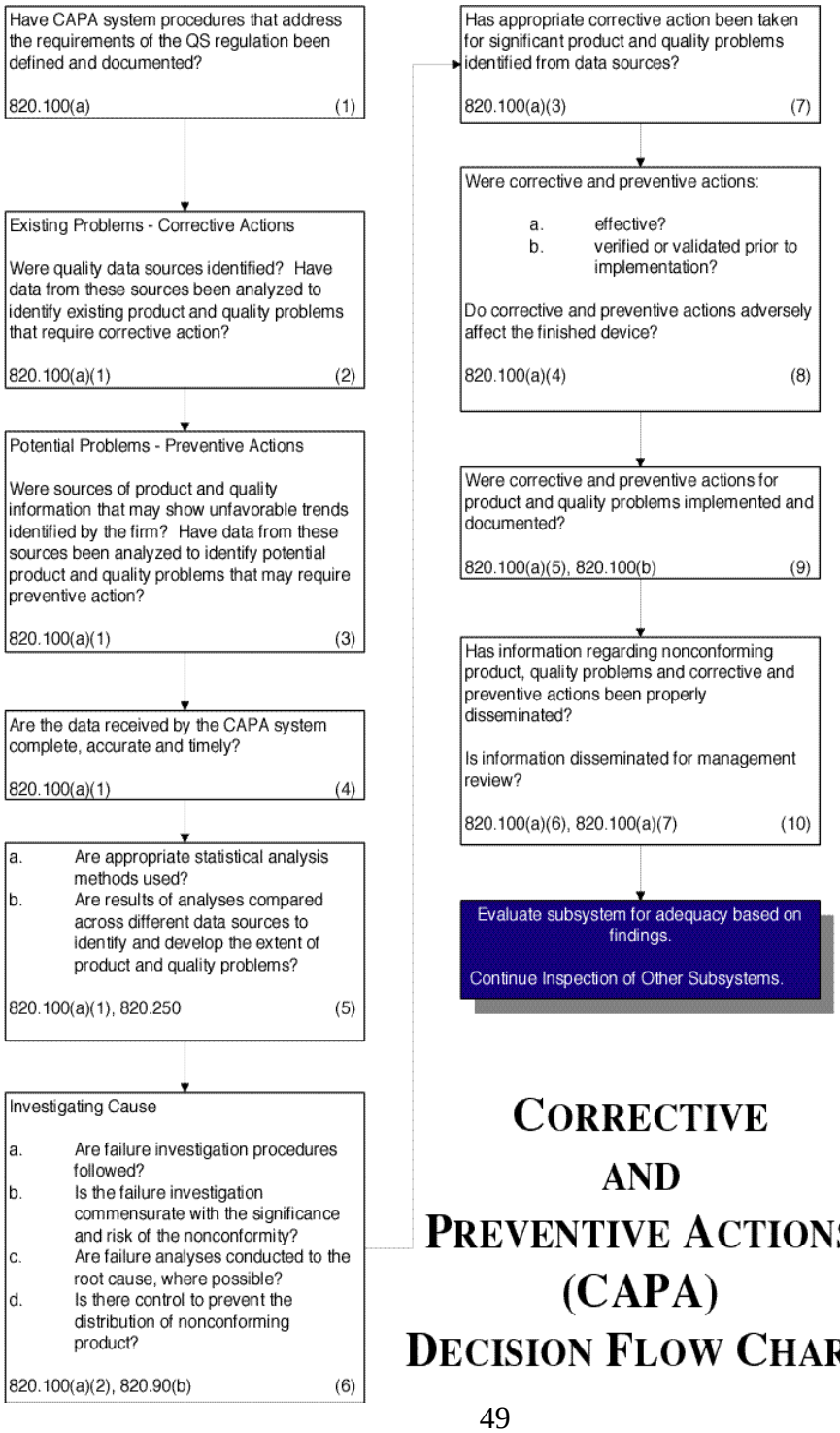
6. Determine if failure investigation procedures are followed. Determine if the degree to which a quality problem or nonconforming product is investigated is commensurate with the significance and risk of the nonconformity. Determine if failure investigations are conducted to determine root cause (where possible). Verify that there is control for preventing distribution of nonconforming product.

7. Determine if appropriate actions have been taken for significant product and quality problems identified from data sources.

8. Determine if corrective and preventive actions were effective and verified or validated prior to implementation. Confirm that corrective and preventive actions do not adversely affect the finished device.

9. Verify that corrective and preventive actions for product and quality problems were implemented and documented.

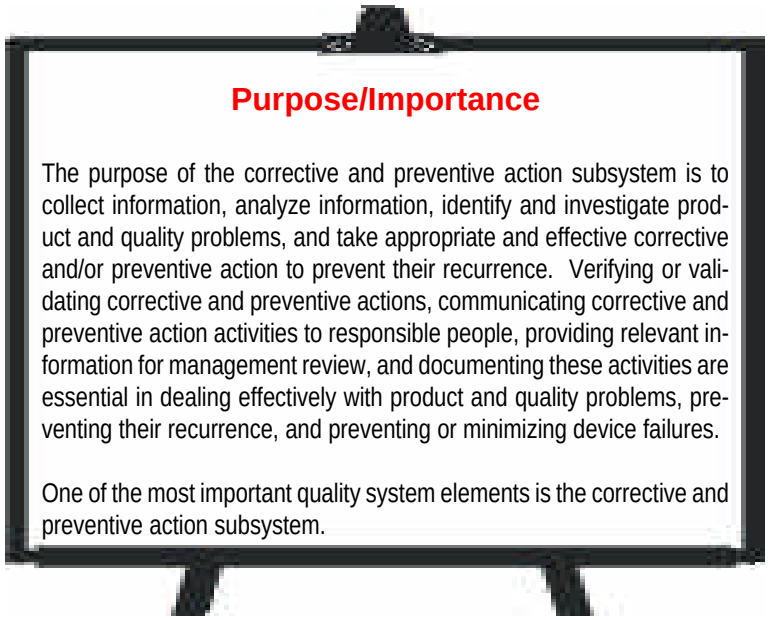
10. Determine if information regarding nonconforming product and quality problems and corrective and preventive actions has been properly disseminated, including dissemination for management review.



CORRECTIVE AND PREVENTIVE ACTIONS (CAPA) DECISION FLOW CHART

Corrective and Preventive Actions (CAPA)

Narrative



1. Verify that CAPA system procedure(s) that address the requirements of the quality system regulation have been defined and documented.

Review the firm's corrective and preventive action procedure. If necessary, have management provide definitions and interpretation of words or terms such as “nonconforming product”, “quality audit”, “correction”, “prevention”, “timely”, and others. It is important to gain a working knowledge of the firm's corrective and preventive action procedure before beginning the evaluation of this subsystem.

NOTE: Corrective action taken to address an existing product or quality problem should include action to:

- Correct the existing product nonconformity or quality problems and;
- Prevent the recurrence of the problem.

The CAPA procedure should include procedures for how the firm will meet the requirements for all elements of the CAPA subsystem. All procedures should have been implemented.

Once you have gained a knowledge of the firm's corrective and preventive action procedure, begin with determining if the firm has a system for the identification and input of quality data into the CAPA subsystem. Such data includes information regarding product and quality problems (and potential problems) that may require corrective and/or preventive action.

2. Determine if appropriate sources of product and quality problems have been identified. Confirm that data from these sources are analyzed to identify existing product and quality problems that may require corrective action.

The firm should have methods and procedures to input product or quality problems into the CAPA subsystem. Product and quality problems should be analyzed to identify product and quality problems that may require corrective action.

The firm should routinely analyze quality data regarding product and quality problems. This analysis should include data and information from all acceptance activities, complaints, service, and returned product records. Determine

NOTE: In accordance with Agency policy (CPG 7151.02), do not request records regarding the results of internal quality audits, management reviews, third party audits (including ISO audits), or supplier audits. However, you will be reviewing raw data that is used by the firm when conducting their quality audits, management reviews, etc. Trending information and results of analyses are generally part of evaluations under the corrective and preventive action requirements. This information is utilized in internal audits and management reviews. Information or data utilized in internal audits and management reviews are considered raw data and should be available for routine review.

if the firm is capturing and analyzing data from acceptance activities relating to component, in-process and finished device testing. Information obtained subsequent to distribution, which includes complaints, service activities and returned products, as well as information relating to concessions (quality and nonconforming products), quality records, and other sources of quality data should also be captured and analyzed. Examples of other sources of quality data include quality audits, installation reports, lawsuits, etc.

3. Determine if sources of product and quality information that may show unfavorable trends have been identified. Confirm that data from these sources are analyzed to identify potential product and quality problems that may require preventive action.

Determine if the firm is identifying product and quality problems that may require a preventive action. This can be accomplished by reviewing historical records such as trending data, corrective actions, acceptance activities (component history records, process control records, finished device testing, etc.) and other quality system records for unfavorable trends. Review if preventive actions have been taken regarding unfavorable trends recognized from the analysis of product and quality information. Product and quality improvements and use of appropriate statistical process control techniques are evidence of compliance with the preventive action requirement.

Determine if the firm is capturing and analyzing data regarding in-conformance product. Examples include capturing and analyzing component test results to detect shifts in test results that may indicate changes in vendor processes, component design or acceptance procedures. Identification of these indicators may necessitate a vendor investigation as a preventive action. Monitoring in-process

and finished device test results may reveal additional indicators of potential quality problems. For devices where stability is an issue, test results of reserve samples are continually monitored. These monitoring activities may trigger process changes, additional training activities and other changes required to maintain the process within its tolerances and limits.

Determine if the firm is using statistical control techniques for process controls where statistical techniques are applicable. An example would be "Statistical Process Control" (SPC). SPC is utilized to monitor a process and initiate process correction when a process is drifting toward a specification limit. Typically, SPC activities are encountered with large volume production processes such as plastic molding and extrusion. Any continuing product improvements (in the absence of identified product problems such as nonconforming product) are also positive indicators of preventive actions. Important linkages for this activity include 820.70 Production and Process Controls and 820.250 Statistical Techniques.

4. Challenge the quality data information system. Verify that the data received by the CAPA system are complete, accurate and timely.

Select one or two quality data sources. Using the sampling tables, review records from the chosen data sources to determine if the data were entered into the CAPA system. In addition, determine whether the data are complete, accurate and entered into the CAPA system in a timely manner.

Important linkages for this activity include 820.80 Acceptance Activities, 820.90 Nonconforming Product, 820.170 Installation, 820.198 Complaint Files and 820.200 Servicing.

5. Verify that appropriate statistical methods are employed (where necessary) to detect recurring quality problems. Determine if results of analyses are compared across different data sources to identify and develop the extent of product and quality problems.

The analysis of product and quality problems should include appropriate statistical and non-statistical techniques. Statistical techniques include Pareto analysis, spreadsheets, and pie charts. Non-statistical techniques include quality review boards, quality review committees and other methods.

The analysis of product and quality problems should also include the comparison of problems and trends across different data sources to establish a global, and not an isolated view, of a problem. For example, problems noted in service records should be compared with similar problem trends noted in complaints and acceptance activity information.

The full extent of a problem must be captured before the probability of occurrence, risk analysis and the proper course of corrective or preventive action can be determined.

6. Determine if failure investigation procedures are followed. Determine if the degree to which a quality problem or nonconforming product is investigated is commensurate with the significance and risk of the nonconformity. Determine if failure investigations are conducted to determine root cause (where possible). Verify that there is control for preventing distribution of nonconforming product.

Review the firm's CAPA procedures for conducting failure investigations. Determine if the procedures include provi-

sions for identifying the failure modes, determining the significance of the failure modes (using tools such as risk analysis), the rationale for determining if a failure analysis should be conducted as part of the investigation, and the depth of the failure analysis.

Discuss with the firm their rationale for determining if a corrective or preventive action is necessary for an identified trend regarding product or quality problems. The decision process may be linked to the results of a risk analysis and essential device outputs.

Using the sampling tables, select failure investigation records regarding more than one failure mode (if possible) and determine if the firm is following their failure investigation procedures.

Confirm that all of the failure modes from your selected sample of failure investigations have been captured within data summaries such as reports, pie charts, spreadsheets, Pareto charts, etc.

Determine whether the depth of the investigation (where possible) is sufficient (root cause) to determine the corrective action necessary to correct the problem. Select one significant failure investigation that resulted in a corrective action and determine if the root cause had been identified so that verification or validation of the corrective action could be accomplished.

Using the sampling tables, review a number of incomplete failure investigations for potential unresolved product nonconformances and potential distribution of nonconforming product. Unresolved problems that could be of significant risk to the patient or user may require product recall if the problem cannot be resolved.

Using the sampling tables, review records regarding nonconforming product where the firm concluded corrective or preventive action was not necessary. As noted above, verify that the firm is not continuing to distribute nonconforming product. This may be an important deficiency based on the class of, and the risk associated with, the product. Important linkages for these activities include 820.20 Management Responsibility, 820.25 Training, 820.30 Design Controls, 820.90 Nonconforming Product and possibly 820.250 Statistical Techniques.

Using the sampling tables, review nonconforming product and quality concessions. Review controls for preventing distribution of nonconforming products. Product and quality concessions should be reviewed to verify that the concessions have been made appropriate to product risk, within the requirements of the quality system and not solely to fulfill marketing needs. Important linkages regarding these activities include 820.20 Management Responsibility and 820.90 Nonconforming Product.

7. Determine if appropriate actions have been taken for significant product and quality problems identified from data sources.

Where appropriate, this may include recall actions, changes in acceptance activities for components, in-process and finished devices, etc.

Using the sampling tables, select and review significant corrective actions and determine if the change or changes could have extended beyond the action taken. A significant action would be a product or process change to correct a reliability problem or to bring the product into conformance with product specifications. Discuss with the firm their rationale for not extending the action to include additional actions such as changes in component supplier, train-

ing, changes to acceptance activities, field action or other applicable actions. Investigators should discuss and evaluate these issues but be careful not to say anything that could be construed as requesting a product recall.

8. Determine if corrective and preventive actions were effective and verified or validated prior to implementation. Confirm that corrective and preventive actions do not adversely affect the finished device.

Using the selected sample of significant corrective and preventive actions, determine the effectiveness of these corrective or preventive actions. This can be accomplished by reviewing product and quality problem trend results. Determine if there are any similar product or quality problems after the implementation of the corrective or preventive actions. Determine if the firm has verified or validated the corrective or preventive actions to ensure that such actions are effective and do not adversely affect the finished device.

Corrective actions must be verified and (if applicable) validated. Corrective actions must include the application of design controls if appropriate.

Good engineering principles should include: establishing a verification or validation protocol; verification of product output against documented product requirements and specifications; ensuring test instruments are maintained and calibrated; and that test results are maintained, available and readable. Important linkages regarding this CAPA element include 820.30 Design Control and 820.70(b) Production and Process Control.

9. Verify that corrective and preventive actions for product and quality problems were implemented and documented.

Using the sampling tables, select and review records of the most recent corrective or preventive actions (this sample may consist of or include records from the previously selected sample of significant corrective actions). To determine if corrective and preventive actions for product and quality problems and changes have been documented and implemented it may be necessary to view actual processes, equipment, facilities or documentation.

10. Determine if information regarding nonconforming product and quality problems and corrective and preventive actions has been properly disseminated, including dissemination for management review.

Determine that the relevant information regarding quality problems, as well as corrective and preventive actions, has been submitted for management review. This can be accomplished by determining which records in a recent CAPA event were submitted for management review. Review the raw data submitted for management review and not the actual results of a management review.

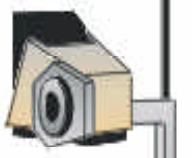
Review the CAPA (and other procedures if necessary) and confirm that there is a mechanism to disseminate relevant CAPA information to those individuals directly responsible for assuring product quality and the prevention of quality problems.

Review information related to product and quality problems that has been disseminated to those individuals directly responsible for assuring product quality and the prevention of quality problems. Using the sample of records from Objective 9 above, confirm that information related to product

and quality problems is disseminated to individuals directly responsible for assuring product quality and the prevention of quality problems.

An important linkage to this CAPA element is 820.20 Management Responsibility.

Corrective and Preventive Actions (CAPA)



Medical Device Reporting

Medical Device Reporting

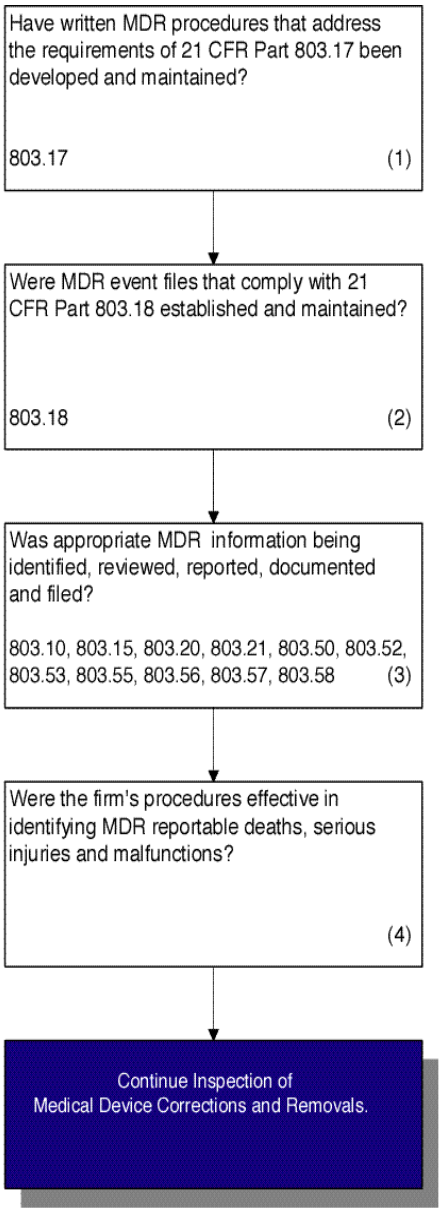
Inspectional Objectives

1. Verify that the firm has MDR procedures that address the requirements in 21 CFR Part 803.17.

2. Verify that the firm has established and maintains MDR event files that comply with 21 CFR Part 803.18.

3. Confirm that the appropriate MDR information is being identified, reviewed, reported, documented and filed.

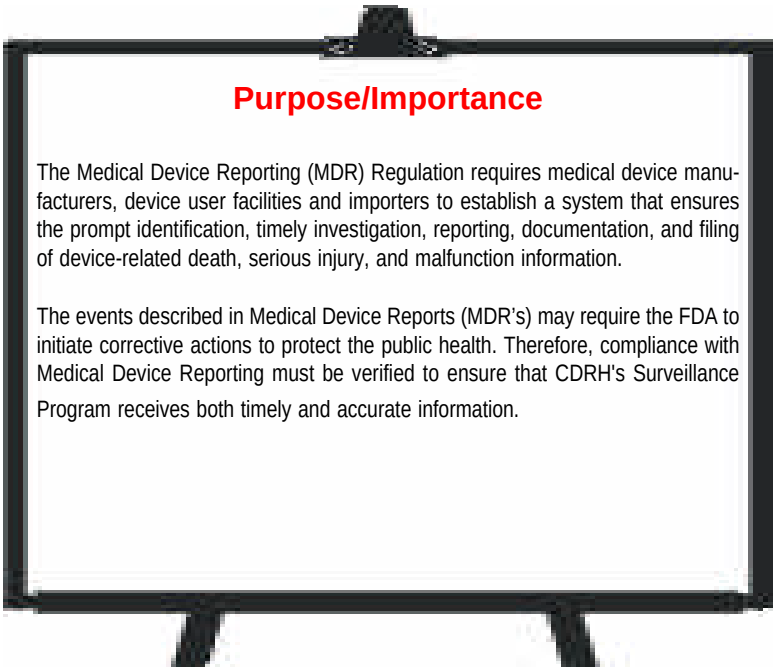
4. Confirm that the firm follows their procedures and they are effective in identifying MDR reportable deaths, serious injuries and malfunctions.



MEDICAL DEVICE REPORTING DECISION FLOW CHART

Medical Device Reporting

Narrative



1. Verify that the firm has MDR procedures that address the requirements in 21 CFR Part 803.17.

Review and confirm that the firm's ***written*** MDR procedures address:

A. ***Internal systems*** that provide for the timely and effective identification, communication, and evaluation of events that may be subject to medical device reporting.

B. ***A standard review process/procedure*** for determining when an event meets the criteria for MDR reporting and ensuring the timely transmission of complete device reports to FDA.

C. ***Documentation and recordkeeping*** regarding: information evaluated to determine if an event is reportable; all MDR reports and other information submitted to the FDA; and systems that ensure access to information that facilitates timely follow-up and inspection by FDA.

2. Verify that the firm has established and maintains MDR event files that comply with 21 CFR Part 803.18

Using the sampling tables, select a number of MDR event files. Review and verify that the MDR event files (hard copy or electronic) are prominently identified and easy to access. MDR files may be maintained as part of the 820.198 complaint file ***IF*** the two aforementioned criteria are met.

Confirm that the MDR event files contain: information from any source that describes a device-related death, serious injury or malfunction; the firm's evaluation of this information including decisions to submit or not to submit an MDR report; and copies or references to supporting documentation (e.g., failure analysis, lab reports, etc.).

Decisions not to submit an MDR report for a device-related death, serious injury or malfunction must be documented in the MDR file.

When applicable, the files will also contain copies of MDR death, serious injury, malfunction and five-day reports submitted on FDA form 3500A, Supplemental Reports (3500A), Baseline Reports (3417) and MDR-related correspondence.

3. Confirm that the appropriate MDR information is being identified, reviewed, reported, documented and filed.

Using the sampling tables, select a number of MDR reports that were submitted to the FDA.

Compare the firm's written procedures to the way it identified, processed, evaluated, reported and filed the reports. Note any discrepancies between the firm's practice/written procedures and any failure to follow or obtain information required by the regulation and form 3500A (e.g., timely reporting, complete investigation, consistency, etc.)

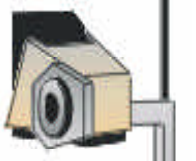
4. Confirm that the firm follows their procedures and they are effective in identifying MDR reportable deaths, serious injuries and malfunctions.

Using the sampling tables, select a number of unreported complaints and records from one additional source of quality data (service reports, repair reports, returned goods files, etc.).

Review these records and confirm that they do not contain information relating to MDR reportable events (device-related deaths, serious injuries or malfunctions).

If unreported events are identified, determine the firm's rationale for not submitting MDR reports. If the firm has failed to identify these events, or does not provide an adequate rationale for not submitting an MDR report (an adequate rationale may be that the firm's investigation determined that it was in fact another manufacturer's device involved in the event), then this may be a significant MDR related observation.

Corrective and Preventive Actions (CAPA)



Reports of Corrections and Removals

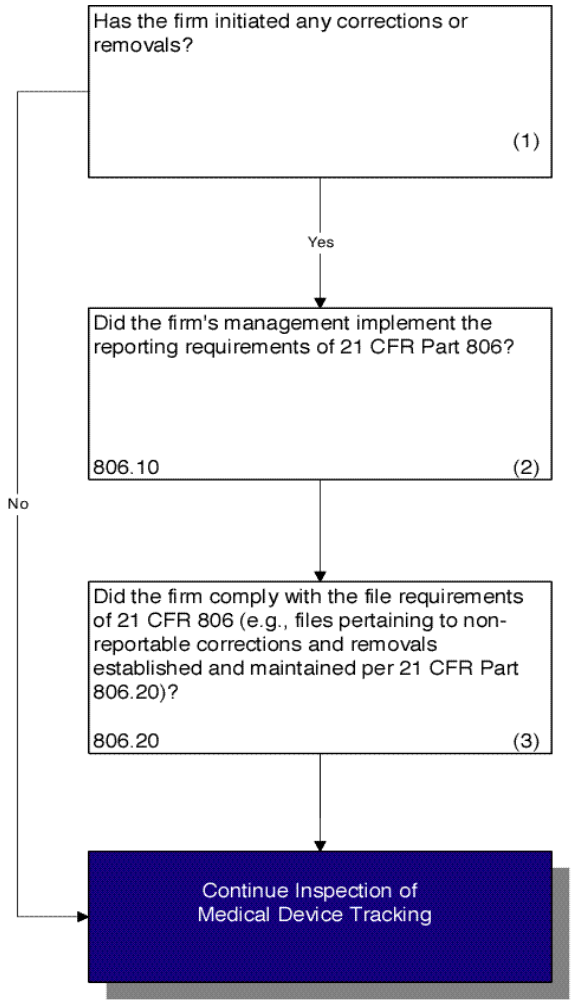
Reports of
Corrections and Removals

Inspectional Objectives

1. Determine if corrections or removals of a device were initiated by the manufacturer.

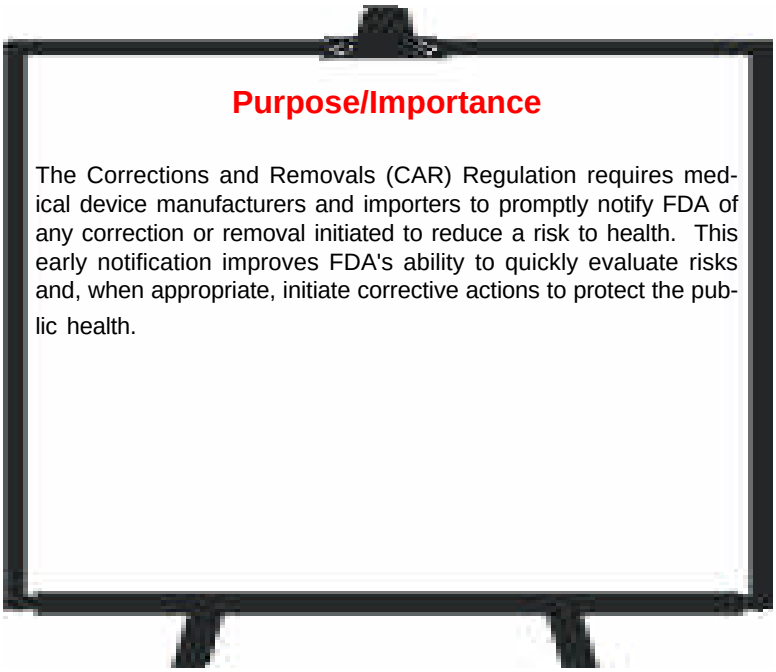
2. Confirm that the firm's management has implemented the reporting requirements of 21 CFR Part 806.

3. Verify that the firm has established and continues to maintain a file for all non-reportable corrections and removals per 21 CFR Part 806.20. Also verify that the firm is complying with the other file-related requirements of 21 CFR Part 806.



REPORTS OF CORRECTIONS AND REMOVALS DECISION FLOW CHART

Reports of
Corrections and Removals



Purpose/Importance

The Corrections and Removals (CAR) Regulation requires medical device manufacturers and importers to promptly notify FDA of any correction or removal initiated to reduce a risk to health. This early notification improves FDA's ability to quickly evaluate risks and, when appropriate, initiate corrective actions to protect the public health.

Narrative

1. Determine if corrections or removals of a device were initiated by the manufacturer.

If the firm has not initiated any corrections or removals, no inspection under Reports of Corrections and Removals is necessary, proceed to the inspection of Medical Device Tracking. However, state in the EIR that Reports of Corrections and Removals were considered for inspection.

If the firm has initiated any corrections or removals, proceed to Objective 2.

2. Confirm that the firm's management has implemented the reporting requirements of 21 CFR Part 806.

Using the sampling tables, select a number of files relating to corrections or removals that have been reported to the FDA.

Review the files and verify that the firm: (1) is submitting written correction and removal reports to the appropriate FDA District Office within 10 days of initiating the actions; and (2) has provided all the information required in the written report per 806.10.

Using the sampling tables, select a number of corrective action files in general (e.g., CAPA files). Review the files. If you identify any apparent Class I or Class II recalls that have not been reported to the appropriate FDA District Office, discuss the discrepancy with the firm. It may be necessary to list unresolved discrepancies on your FDA 483. All observations must be consistent with current FDA policies and procedures.

3. Verify that the firm has established and continues to maintain a file for all non-reportable corrections and removals per 21 CFR Part 806.20. Also verify that the firm is complying with the other file-related requirements of 21 CFR Part 806.

Using the sampling tables, select a number of files relating to non-reportable corrections or removals (806.20 files).

NOTE: Part 806 does not require firms to establish and maintain files for corrections and removals reported to the FDA. However, documentation of corrective actions is required by the Quality System Regulation (21 CFR 820.100, Corrective and Preventive Action and 21 CFR 820.198, Complaint Files).

Review the 806.20 files and verify that the records contain all the information required in 806.20. This review must include confirmation that the files are retained for the appropriate period of time (2 years beyond the expected life of the device).

Confirm that these files also do not contain evidence of unreported (apparent) Class I or Class II recalls. Determine whether the files contain evidence of unreported (apparent) Class III voluntary recalls under 21 CFR Part 7. Also, verify that the firm is complying with the other file-related requirements of 21 CFR Part 806.

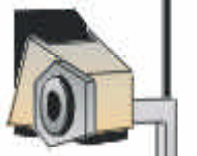
Confirm any claims for exemption from 806 as a result of a submission under either the MDR regulation or Radiological Health requirements. If you need assistance, contact the District Recall Coordinator.

If the device has been sold to another firm, verify that the 806.20 files have been transferred to the new manufacturer or importer.

If compliance with the above requirements cannot be confirmed, discuss the discrepancy with the firm. It may be necessary to list unresolved discrepancies on your FDA 483. All observations must be consistent with current FDA policies and procedures.

NOTE: If the device has been sold to a firm that is not in your District, forward an assignment request to the appropriate District Office requesting confirmation that the 806.20 files have been transferred to the new manufacturer or importer.

Corrective and Preventive Actions (CAPA)



Medical Device Tracking

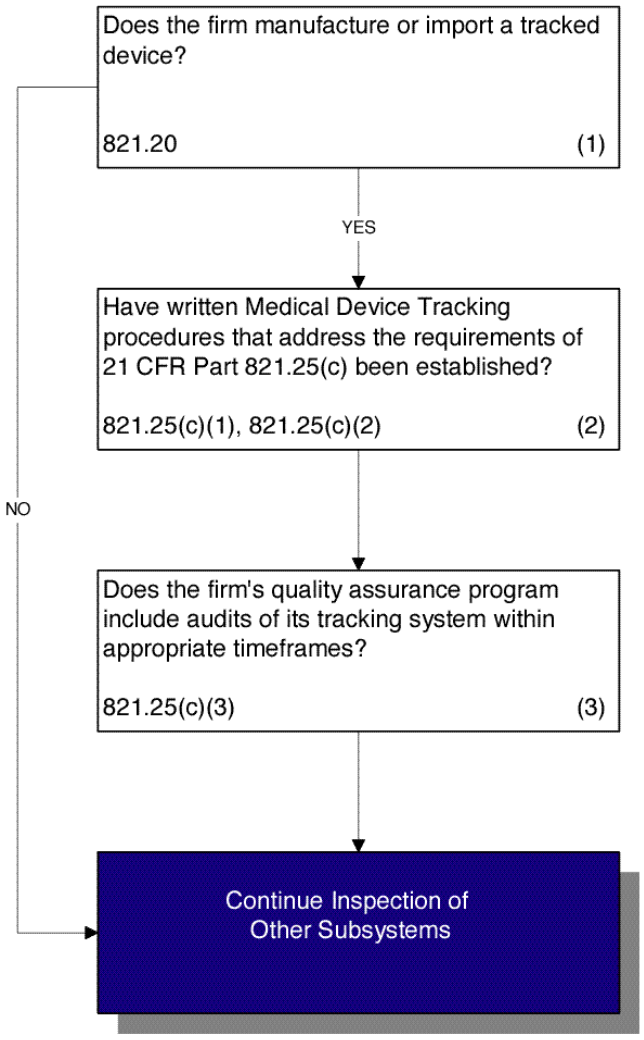
Medical Device Tracking

Inspectional Objectives

1. Determine if the firm manufactures or imports a tracked device.

2. Verify that the firm has established a written standard operating procedure (SOP) for tracking that complies with the requirements in 21 CFR Part 821.25(c).

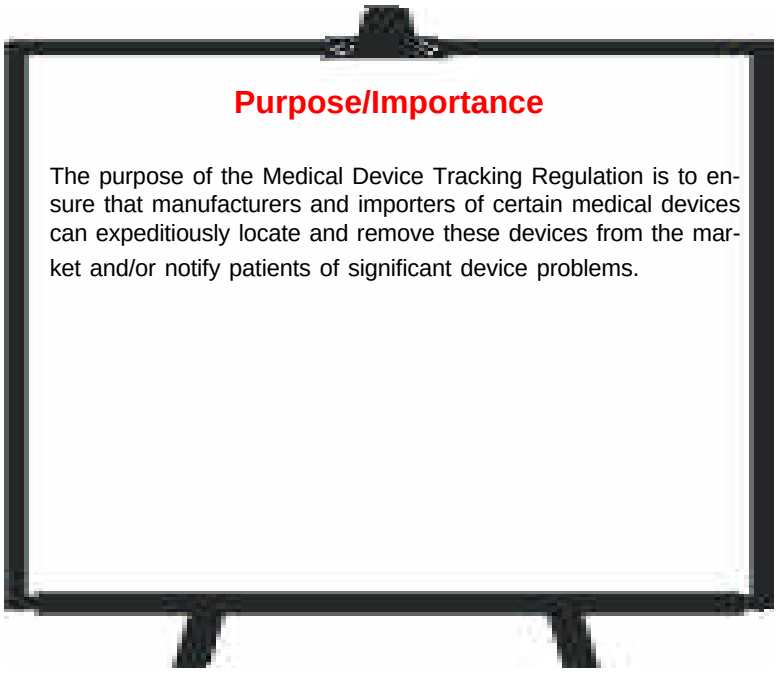
3. Verify that the firm's quality assurance program includes audits of its tracking system within the appropriate time-frames specified in 21 CFR Part 821.25(c)(3).



MEDICAL DEVICE TRACKING DECISION FLOW CHART

Medical Device Tracking

Narrative



1. Determine if the firm manufactures or imports a tracked device.

Ask the Management Representative (or designee) whether the firm manufactures or imports any device subject to the Medical Device Tracking Regulation (21 CFR Part 821). If the firm ***does not*** manufacture or import a device subject to the tracking regulation, you can terminate your tracking inspection.

If the firm ***does*** manufacture or import a device subject to the tracking regulation, verify via discussions with the Management Representative (or designee) or the review of es-

tablished procedures, that the firm is aware of its tracking obligations.

Verify that the firm is aware of its obligation to: (1) notify FDA if it goes out of business and provide copies of its tracking records to its FDA District Office; (2) transfer tracking records to a firm purchasing its tracked device(s); and (3) continue tracking a device the firm stops manufacturing or importing if the firm remains in business.

If the firm's tracked device was purchased from another firm, confirm (where applicable) that the firm has obtained and maintains the prior manufacturer's tracking records or equivalent information.

2. Verify that the firm has established a written standard operating procedure (SOP) for tracking that complies with the requirements in 21 CFR Part 821.25(c).

Review the firm's written tracking SOP(s) and confirm (if possible) that they address the firm's capability to: (1) identify the location and other required data, for tracked devices ***undistributed to a patient within three working days*** after a request by FDA, and (2) identify the location and other required data for tracked devices ***distributed to a patient***, ***within 10 working days*** after receipt of a request from FDA.

If applicable, select one or two files containing tracking information requested by the FDA and confirm that the appropriate information required by 821.25(a)(1) – 821.25(a)(3) was provided within the appropriate time-frame(s).

Confirm that the written tracking SOP(s) address the remaining 821.25(a), 821.25(b), and 821.25(c) requirements for the collection, maintenance and auditing of tracking data.

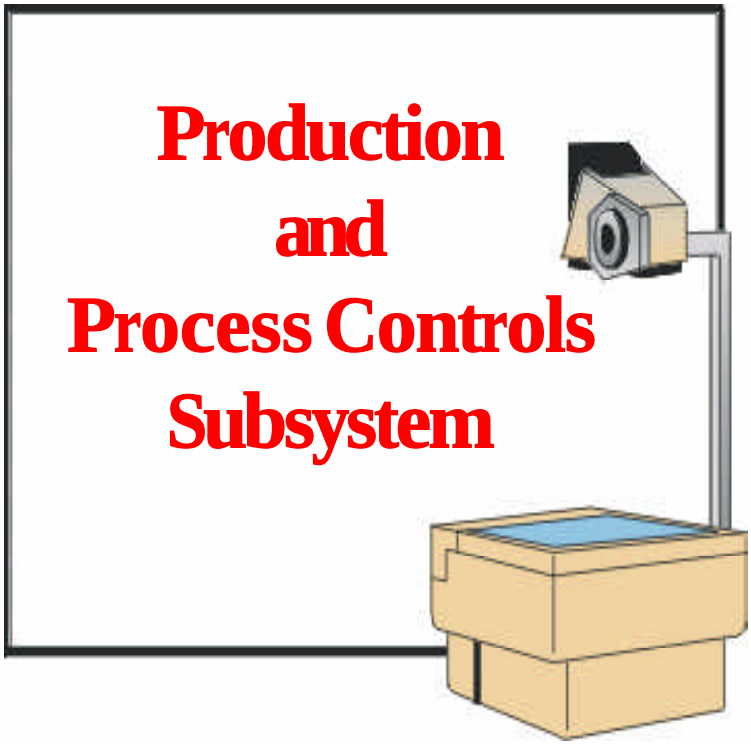
3. Verify that the firm's quality assurance program includes audits of its tracking system within the appropriate time-frames specified in 21 CFR Part 821.25(c)(3).

Confirm that the audit procedure addresses both the functioning of the tracking system and the accuracy and completeness of the data within the system.

Confirm that the firm has conducted audits of its tracking system at the appropriate time intervals (no less than every six months for the first three years of tracking and annually thereafter).

NOTE: The agency's policy relative to the review of quality audit results is stated in CPG 7151.02 (CPG Manual Sub Chapter 130.300). This policy prohibits FDA access to a firm's quality audit results. However, the audit procedures and documents that demonstrate that the audits have been conducted at the appropriate time intervals are subject to FDA inspection.

Production and Process Controls Subsystem



Production and Process Controls

Inspectional Objectives

1. Select a process for review based on:

    a. CAPA indicators of process problems;
    b. Use of the process for manufacturing higher risk devices;
    c. Degree of risk of the process to cause device failures;
    d. The firm's lack of familiarity and experience with the process;
    e. Use of the process in manufacturing multiple devices;
    f. Variety in process technologies and Profile classes;
    g. Processes not covered during previous inspections;
    h. Any other appropriate criterion as dictated by the assignment

Note: If the process chosen is sterilization, evaluate the process according to the "Sterilization Process Controls" chapter of this handbook.

2. Review the specific procedure(s) for the manufacturing process selected and the methods for controlling and monitoring the process. Verify that the process is controlled and monitored.

Note: Control and monitoring procedures may include in-process and or finished device acceptance activities as well as environmental and contamination control measures.

3. If review of the Device History Records (including process control and monitoring records, etc.) reveals that the process is outside the firm's tolerance for operating parameters and/or rejects or that product nonconformances exist:

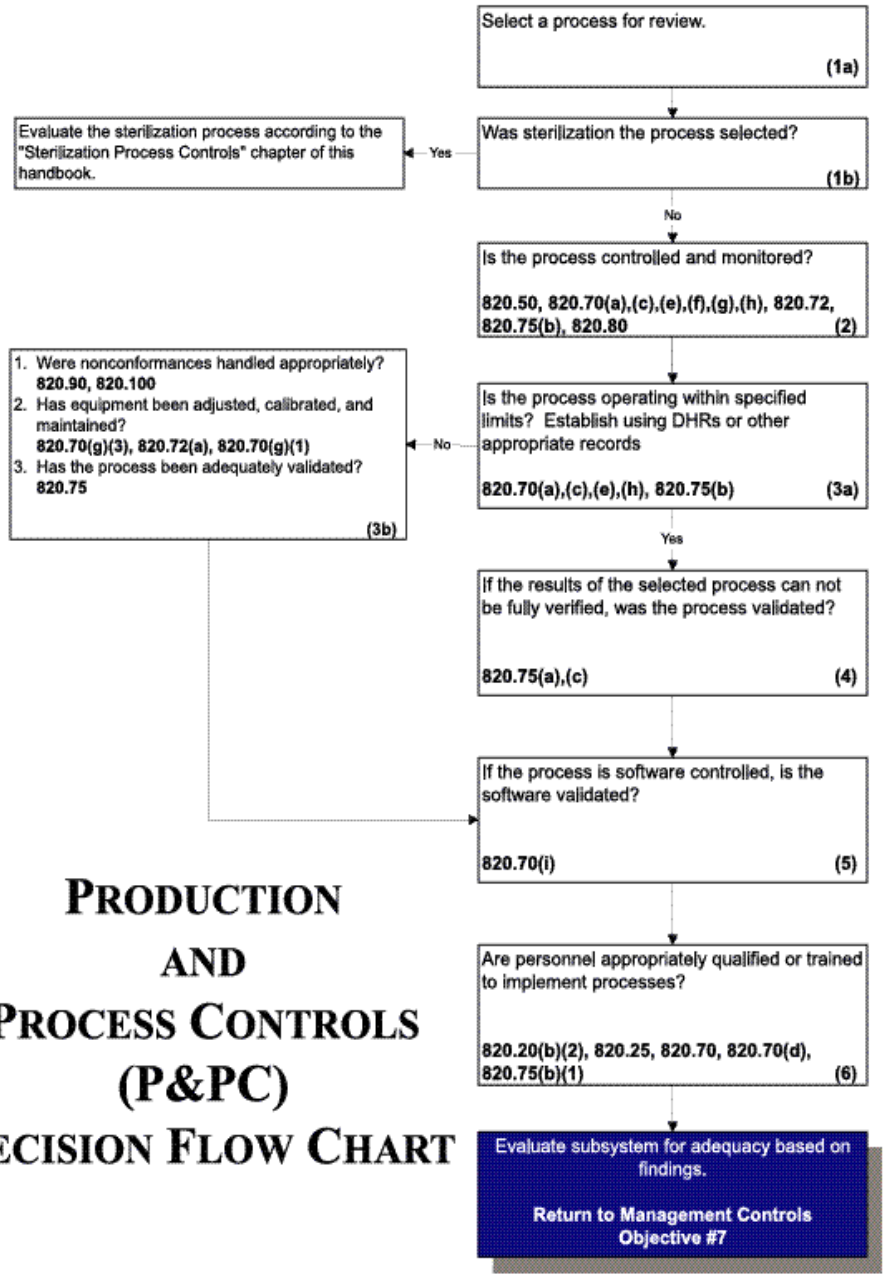
    a. Determine whether any nonconformances were handled appropriately;
    b. Review the equipment adjustment, calibration and maintenance; and
    c. Evaluate the validation study in full to determine whether the process has been adequately validated.

4. If the results of the process reviewed cannot be fully verified, confirm that the process was validated by reviewing the validation study.

5. If the process is software controlled, confirm that the software was validated.

6. Verify that personnel have been appropriately qualified to implement validated processes or appropriately trained to implement processes which yield results that can be fully verified.

PRODUCTION AND PROCESS CONTROLS (P&PC) DECISION FLOW CHART



Production and Process Controls

Narrative

Purpose/Importance

The purpose of the production and process control subsystem is to manufacture products that meet specifications. Developing processes that are adequate to produce devices that meet specifications, validating (or fully verifying the results of) those processes, and monitoring and controlling the processes are all steps that help assure the result will be devices that meet specifications.

1. Select a process for review based on:

a. **CAPA indicators of process problems;**
b. **Use of the process for manufacturing higher risk devices;**
c. **Degree of risk of the process to cause device failures;**
d. **The firm's lack of familiarity and experience with the process;**
e. **Use of the process in manufacturing multiple devices;**
f. **Variety in process technologies and profile classes;**
g. **Processes not covered during previous inspections;**
h. **Any other appropriate criterion as dictated by the assignment**

Note: If the process chosen is Sterilization, evaluate the process according to the "Sterilization Process Controls" chapter of this handbook.

In order to meet the Production and Process Control requirements of the Quality System Regulation, the firm must understand when deviations from device specifications could occur as a result of the manufacturing process or environment.

Discuss with the Management Representative (or designee) the firm's system for determining whether deviations from device specifications could occur as a result of the manufacturing process or environment. The firm may accomplish this requirement via Product and Process Risk Analyses. Important linkages for these activities include 820.20 Management Responsibility and 820.30 Design Controls.

Select for evaluation a manufacturing process where deviations from device specifications could occur as a result of the process or its environment. The selection of the manufacturing process for evaluation should be based upon one or more of the criteria listed above. Important linkages to consider at this point include 820.30 (g) Design Validation (risk analysis) and 820.100 Corrective and Preventive Action.

2. Review the specific procedure(s) for the manufacturing process selected and the methods for controlling and monitoring the process. Verify that the process is controlled and monitored.

Note: Control and monitoring procedures may include in-process and or finished device acceptance activities as well as environmental and contamination control measures.

All processes that may cause a deviation to a device's specification and all validated processes must be monitored and controlled in accordance with established procedures. Just because a process is validated, does not mean verification activities utilized to monitor and control the process are unnecessary. Examples of some verification activities associated with validated processes include review of process parameters, dimensional inspections, package performance tests, sterility and EO residual testing.

For the process chosen, confirm that the established Process (and where applicable Environmental and Contamination) Control, Monitoring and Product Acceptance Procedures maintained by the shop floor are the most current approved revision contained within the Device Master Record (DMR). Most firms maintain a "Master List" of the most currently approved documents. This list can be verified against the DMR and brought to the shop floor to compare with the currently available documents.

Verify that the building is of suitable design and contains sufficient space to perform necessary operations.

Verify that the control and monitoring activities demonstrate that the process is currently operating in accordance with the DMR. This should be done on the shop floor by reviewing work instructions, product acceptance criteria and results, control charts, etc.

While on the shop floor, make note of one significant piece of process equipment and one significant piece of inspection, measuring or test equipment (preferably from a finished device acceptance activity). Prior to concluding the

NOTE: Control and monitoring procedures may include in-process and/or finished device acceptance activities as well as environmental and contamination control measures.

inspection, confirm that applicable maintenance activities (preventive maintenance, cleaning, adjustment etc.) are performed as scheduled for the chosen piece of processing equipment. Also confirm that the piece of inspection, measuring or test equipment was controlled and calibrated.

Once you've reviewed the process control and monitoring activities on the shop floor, use the sampling tables and select for review a number of Device History Records (DHR's including monitoring and control records, etc.) from recent production runs. If the process is run over more than one shift, your review should include DHR's from all shifts. Verify that the product was manufactured in accordance with the Device Master Record.

This verification must include a review of the purchasing controls and receiving acceptance activities regarding at least one component or raw material (preferably determined essential for the proper functioning of the device).

In addition, this verification must include a review of in-process and final finished device acceptance activities and results as well as environmental and contamination control records (if applicable). Verify that sampling plans for process and environmental control and monitoring activities are based upon a valid statistical rationale.

If your review of the device history records reveals no anomalies proceed to Objective 4.

If evidence that the process or environment are not controlled and monitored (no control and monitoring activities, not operating within most currently approved parameters or reject limits, etc.) is observed, this may be a major production and process control deficiency. Important linkages

to consider at this point include Documents, Records & Change Controls, (820.40 Document Controls, 820.180

Records, 820.181 Device Master Record, 820.184 Device History Record,), Facilities and Equipment Controls (820.72 Inspection, Measuring, and Test Equipment), Material Controls (820.50 Purchasing Controls, 820.60 Identification, 820.65 Traceability, 820.80 Receiving, In-process, and Finished device acceptance, 820.86 Acceptance Status, 820.130 Packaging, 820.140 Handling, 820.150 Storage, 820.160 Distribution) and 820.250 Statistical Techniques.

☑ **3. If review of the Device History Records (including process control and monitoring records, etc.) reveals that the process is outside the firm's tolerance for operating parameters and/or rejects or that product nonconformances exist:**

- **a. Determine whether any nonconformances were handled appropriately;**
- **b. Review the equipment adjustment, calibration and maintenance; and**
- **c. Evaluate the validation study in full to determine whether the process has been adequately validated.**

If process or product nonconformance(s) are identified based upon these activities, determine whether the nonconformance(s) were recognized by the firm, handled appropriately and fed into its CAPA system. Review (if appropriate) the firm's nonconforming product control, review and disposition activities and any CAPA's indicated. If the firm's Quality System failed to recognize the process or

NOTE:

1. If the firm engages in a number of manufacturing processes, Investigators should avoid repeatedly selecting the same process every time the firm is inspected.

2. If Device Labeling is the process chosen, include in your inspection coverage of the requirements of "820.120 Device Labeling".

product nonconformance(s) or take appropriate CAPA, this may be a major CAPA deficiency.

Review the firm's equipment adjustment, maintenance and calibration records for the process and (if appropriate) comprehensively evaluate the Validation Study as described in the "Note" contained within the narrative discussion of Objective 4. These activities may provide further insight into the cause of the nonconformance. If the firm has recognized and implemented appropriate CAPA's regarding the observed nonconformance(s), then the quality system was effective. Proceed to Objective 5. Important linkages to consider at this point include Corrective and Preventive Action, Material Controls (820.90 Nonconforming product), and Facilities and Equipment Controls (820.72 Control of inspection, measuring and test equipment).

4. If the results of the process reviewed cannot be fully verified, confirm that the process was validated by reviewing the validation study.

If the results of the process *can* be fully verified, proceed to Objective 5.

If the chosen process requires process validation, review the established Process Validation Procedure(s). The regulation does not require a general Process Validation Procedure. Therefore, separate procedures may be established for each individual Process Validation Study. Remember, the definition of "Product" contained within the regulation includes components, in-process devices and finished devices. Verify via a review of the Process Validation Study Summary (if available) and Approval, that objective evidence has demonstrated that the process will consistently generate a product or result meeting its predetermined specifications. With respect to process validation, an ex-

ample of a "result" is a Sterility Assurance Level (SAL). If a Validation Study Summary and Approval is not available, a review of objective evidence within the validation study will be necessary.

NOTE: If there are indications (via review of DHR's, the Process Validation Study Summary and Approval, the assignment, CAPA system, etc.) of unresolved, potential problems with a validated process, in addition to a review of process monitoring and control activities, a comprehensive validation study review should be conducted. This review should include determining whether: 1. The instruments used to generate the objective evidence were properly calibrated and maintained prior to the validation study; 2. Predetermined product specifications were established; 3. Test sample sampling plans were based upon a statistically valid rationale; 4. Objective evidence demonstrates predetermined product specifications were met consistently; 5. Process tolerance limits were challenged; 6. Process equipment was properly installed, adjusted and maintained; 7. Process monitoring instruments are properly calibrated and maintained; 8. Changes to the validated process were appropriately challenged; and, 9. Process operators are appropriately qualified.

If the objective evidence demonstrates that the process is not capable of consistently producing a product or result meeting its predetermined specifications, this is a major process validation deficiency. Important linkages to consider at this point include Management Responsibility (including 820.25 Personnel), Design Controls (820.30(h) Design Transfer), Corrective and Preventive Action, and Facilities and Equipment Controls (820.72 Inspection, Measuring and Test Equipment) and 820.250 Statistical Techniques.

5. If the process is software controlled, confirm that the software was validated.

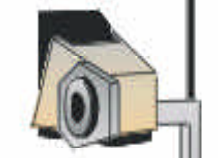
If the process chosen is *NOT* controlled with software, proceed to Objective 6.

If the process chosen is automated with software, review the software requirements document, software validation protocol, software validation activities, software change controls and software validation results to confirm that the software will meet user needs and its intended use. If multiple software driven systems are used in the process, challenge one based upon significance. An important linkage to consider at this point is Material Controls (820.50 Purchasing Controls). For example, for software developed elsewhere, confirm that appropriate software and quality requirements were established and provided to the vendor and that purchasing data (and validation results) support that the requirements were met.

6. Verify that personnel have been appropriately qualified to implement validated processes or appropriately trained to implement processes which yield results that can be fully verified.

Using the sampling tables, select a number of training and qualification records for process operators and employees conducting Q.C. activities related to the chosen process. Where a process is operated over more than one shift, training records from all shifts should be included within your review. Confirm that the employees are aware of the device defects that may occur as a result of improper performance of their assigned responsibilities. Confirm that employees conducting Q.C. inspections and tests are aware of the defects and errors that may be encountered while performing their assigned responsibilities. An important linkage to consider at this point is Management Responsibility (820.25 Personnel).

Production and Process Controls Subsystem



Sterilization Process Controls

Sterilization Process Controls

Inspectional Objectives

1. Confirm that the sterilization process was validated by reviewing the validation study.

2. Review the specific procedure(s) for the sterilization process selected and the methods for controlling and monitoring the process. Verify that the process is controlled and monitored.

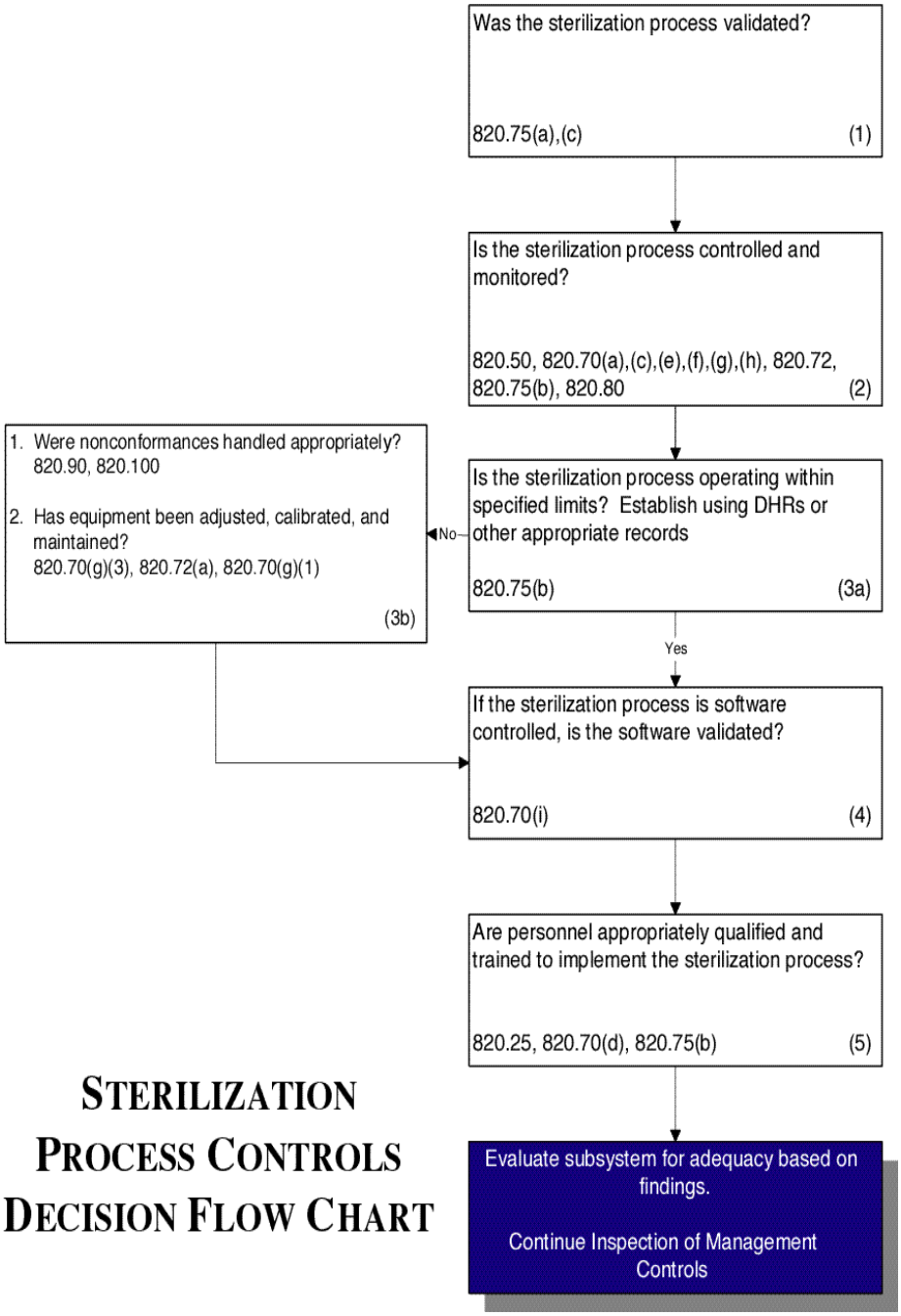
3. If review of the Device History Records (including process control and monitoring records, acceptance activity records, etc.) reveals that the sterilization process is outside the firm's tolerance for operating or performance parameters:

    a. Determine whether the nonconformances were handled appropriately; and
    b. Review the equipment adjustment, calibration and maintenance

4. If the sterilization process is software controlled, confirm that the software was validated.

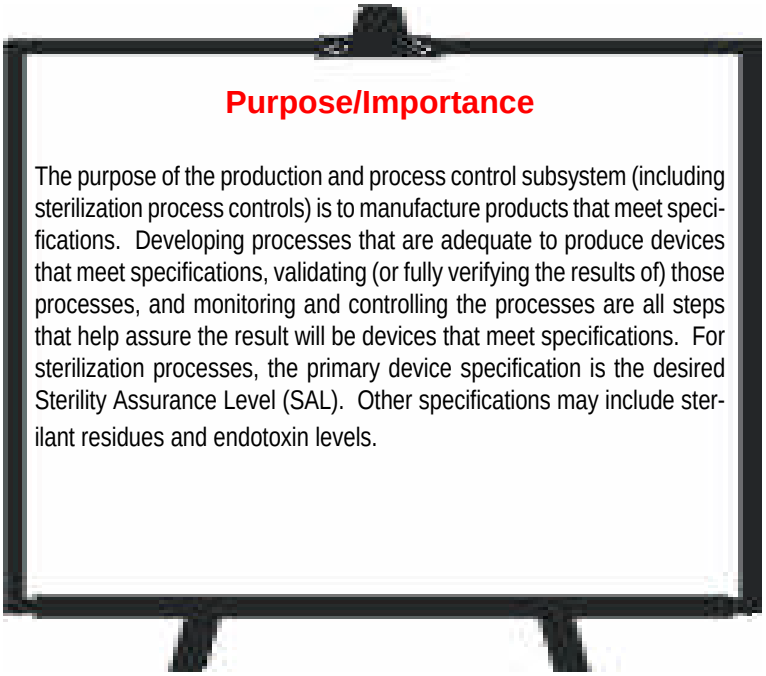
5. Verify that personnel have been appropriately qualified and trained to implement the sterilization process.

STERILIZATION PROCESS CONTROLS DECISION FLOW CHART



Sterilization Process Controls

Narrative



Purpose/Importance

The purpose of the production and process control subsystem (including sterilization process controls) is to manufacture products that meet specifications. Developing processes that are adequate to produce devices that meet specifications, validating (or fully verifying the results of) those processes, and monitoring and controlling the processes are all steps that help assure the result will be devices that meet specifications. For sterilization processes, the primary device specification is the desired Sterility Assurance Level (SAL). Other specifications may include sterilant residues and endotoxin levels.

If you are inspecting a contract sterilizer, Inspectional Objectives 2 through 5, described below, are applicable and must be performed. Inspectional Objective 1 regarding validation is applicable only in so far as the contract sterilizer has assumed any responsibility for validation of the process, as indicated in the written agreement between the device manufacturer and the contract sterilizer.

1. Confirm that the sterilization process was validated by reviewing the validation study.

Validation studies (according to established procedures) are required for sterilization processes.

The review of the sterilization process validation study may be limited to a review of the Validation Study Summary (if available) and Approval if the complete validation study was assessed during the previous inspection and there have been no significant changes in the process, product or package that may impact sterilization effectiveness.

When conducting a complete sterilization process validation study assessment, the items included in the narrative note under Objective 4 of the Production and Process Controls chapter of this Handbook apply. A complete sterilization process validation study assessment must include a review of the established validation procedures and verification (via a review of objective evidence) that: 1. Based upon the bioburden of the product, the defined sterilization process parameters will consistently be effective in obtaining a predetermined Sterility Assurance Level (SAL); and 2. The defined process parameters will not adversely affect product and package performance.

Objective evidence that the sterilization process parameters will consistently be effective in obtaining a predetermined Sterility Assurance Level (SAL) includes records documenting: 1. The determination of product bioburden; 2. The establishment of process parameters and tolerances; 3. The definition of acceptance criteria for a successful validation study; 4. The process challenge studies (e.g. half cycle runs for Ethylene Oxide, verification dose experiments for radia-

NOTE: Many firms sterilize their products according to the guidance provided within consensus standards (e.g. AAMI/ANSI/ISO standards). These standards are specific to various types of sterilization processes. FDA recognizes many of these standards. This means FDA finds them acceptable. A list of recognized sterilization standards appears at FDA's Center for Devices and Radiological Health (CDRH's) web site located at:

www.fda.gov/cdrh/modact/recstand.html

Firms may elect to comply with these standards. However, compliance to the standards is voluntary. When a firm claims to comply with one of the recognized standards, the requirements of the standard must be met. If a firm does not claim to comply with a recognized standard, it must provide a scientific rationale supporting the method used for validating and processing its sterilization loads.

tion, or media fills for aseptic processing); and 5. The results of process control and monitoring and acceptance activities (control charts, Biological Indicators, Dosimeters, etc.) used to demonstrate that predetermined acceptance criteria had been met.

Objective evidence that process parameters will not adversely affect product and package performance include records documenting performance testing of the product and packaging following the sterilization process or multiple sterilization processes (if applicable).

Determine whether periodic assessments (e.g. revalidations, sterility dose audits, etc.) of the adequacy of the sterilization process are conducted. Review the records of one periodic assessment of the adequacy of the sterilization process.

NOTE: Many device manufacturers use contract sterilizers for sterilization of their devices. These manufacturers retain the responsibility for the sterility of the finished devices even though sterilization processing is not performed at their own facilities. Therefore, your inspection of a manufacturer that uses the services of a contract sterilizer must verify that the manufacturer has assumed that responsibility. Inspectional Objectives 1 through 3 are applicable in this situation because the manufacturer must be able to provide to you the documentation regarding sterilization validation and processing of its devices regardless of the location of these activities. Although the manufacturer may not have detailed records regarding Objectives 4 and 5 for the contractor's software and personnel, he must have assured the adequacy of these activities by the contractor, through activities such as an audit of the contractor, visits to the contractor, or review of documentation from the contractor. Objective 5 regarding qualifications of the manufacturer's own Q.C. personnel should be covered during your inspection of the manufacturer.

2. Review the specific procedure(s) for the sterilization process selected and the methods for controlling and monitoring the process. Verify that the process is controlled and monitored.

The sterilization process must be validated. However, this does not mean that verification activities utilized to monitor and control the process are unnecessary.

If performed at this location, confirm that the sterilization process, associated environmental and contamination controls, and monitoring and acceptance procedures maintained by the shop floor are the most current approved revision contained within the Device Master Record (DMR). Most firms maintain a "Master List" of the currently approved documents. This list can be verified against the DMR and brought to the shop floor to compare with the currently available documents.

Verify that the building is of suitable design and contains sufficient space to perform necessary operations.

Verify that the control and monitoring activities demonstrate that the process is currently operating in accordance with the DMR. Sterilization parameters which may need to be monitored and controlled include: time, temperature, pressure, load configuration, and humidity. Several of these parameters may require monitoring and control prior to, during and after sterilization processing (e.g. preconditioning, conditioning and aeration in Ethylene Oxide processing). Verification activities used to monitor and control the sterilization process may include: bioburden testing, Biological Indicator (BI) testing, Chemical Indicator (CI) testing, process control record review, sterilant residue testing, and endotoxin testing.

Additionally, packaging integrity verification activities must be reviewed for every inspection during which sterilization is covered. This review of the control and monitoring activities should be done on the shop floor by reviewing work instructions, product acceptance procedures, control charts, etc.

While on the shop floor, make note of one piece of significant sterilization process equipment and one significant piece of inspection, measuring or test equipment (preferably from a finished device acceptance activity). Prior to concluding the inspection, confirm that the applicable maintenance activities (preventive maintenance, cleaning and adjustment, etc.) are performed as scheduled for the chosen piece of sterilization process equipment. Also, confirm that the piece of inspection, measuring, and test equipment was controlled and calibrated.

After you have reviewed the process control and monitoring activities on the shop floor, use the sampling tables and select for review a number of Device History Records (DHRs, including monitoring and control records, acceptance testing records, etc.) from recent production runs. If the process is run over more than one shift, your review should include DHRs from all shifts. Verify that the product was sterilized in accordance with the DMR. Your review of the selected records should include all applicable verification activities (see above) including records of process parameter monitoring, and in-process and final device acceptance activities and results.

Your evaluation must also include a review of the firm's purchasing controls and receiving acceptance activities regarding at least one component, material or service. Examples include: the sterilant, sterilization indicators, and services provided by contract sterilizers or contract laboratories. In addition, review environmental and contamina-

tion control records (e.g. bioburden sampling, testing and results). Verify that the sampling plans for process and environmental control and monitoring activities are based upon a valid statistical rationale.

If your review of the Device History Records reveals no anomalies, proceed to Objective 4.

If evidence that the process or environment are not controlled and monitored (no control and monitoring activities, not operating within most currently approved parameters, etc.) is observed, this may be a major production and process control deficiency. Important linkages to consider at this point include: Documents, Records and Change Controls (820.180 Records, 820.181 Device Master Record, 820.184 Device History Record, 820.40 Document Controls); Facilities and Equipment Controls (820.72 Inspection, Measuring, and test Equipment); Material Controls (820.50 Purchasing Controls, 820.80 Receiving, In-process, and finished device acceptance, 820.140 Handling, 820.150 Storage, and 820.160 Distribution, and 820.250 Statistical Techniques, 820.60 Identification, 820.65 Traceability, 820.86 Acceptance Status); 820.130 Packaging; and 820.250 Statistical Techniques.

3. If review of the Device History Records (including process control and monitoring records, acceptance activity records, etc.) reveals that the sterilization process is outside the firm's tolerance for operating or performance parameters:

   a. Determine whether the nonconformances were handled appropriately; and
   b. Review the equipment adjustment, calibration and maintenance

If process or product nonconformance(s) are identified

based upon these activities, determine whether the nonconformance(s) were recognized by the firm, handled appropriately and fed into its CAPA system.

Review (if appropriate) the firm's nonconforming product control, review and disposition activities and any CAPA's indicated. If the CAPA included a retest, review the firm's rationale for invalidating the original test results. If the CAPA included resterilization, confirm that the effects of the resterilization process on the product and package are understood. For example, did a validation study provide objective evidence that resterilization was acceptable?

If the firm's Quality System failed to recognize the process or product nonconformance(s) or take appropriate CAPA, this may be a major CAPA deficiency. Review the firm's equipment adjustment, maintenance and calibration records for the process. These activities may provide further insight into the cause of the nonconformances.

Examples of nonconformances and sterilization process failures the investigator may encounter include: Test Failures (e.g. Positive Biological Indicators, high EO residues, high bioburdens, out of specification endotoxin results); Parametric Failures (process failures such as unspecified dwell times, low pressure, low EO gas weights, loss of humidity, etc.); and Packaging Failures. Packaging Failures may be an indication of a sterilization process parameter problem (vacuum) or a packaging process problem (validation, sealer set up, etc.).

Important linkages to consider at this point include Corrective and Preventive Actions, Material Controls (820.90 Nonconforming product), and Facilities and Equipment Controls (820.72 Control of inspection, measuring, and test equipment).

4. If the sterilization process is software controlled, confirm that the software was validated.

If the sterilization process chosen is *NOT* controlled with software, proceed to Objective 5.

If the sterilization process is automated with software, review the software requirements document, software validation protocol, software validation activities, software change controls and software validation results to confirm that the software will meet user needs and its intended use. If multiple software driven systems are used in the sterilization process, challenge one based upon significance. An important linkage to consider at this point is Material Controls (820.50 Purchasing Controls). For example, for software developed elsewhere, confirm that appropriate software and quality requirements were established and provided to the vendor and that purchasing data (and validation results) support that the requirements were met.

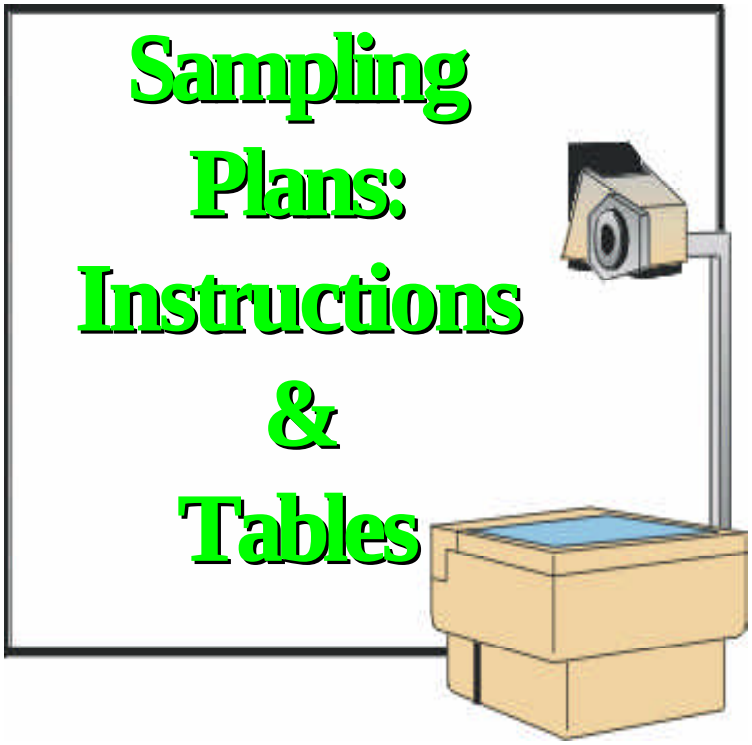
5. Verify that personnel have been appropriately qualified and trained to implement the sterilization process.

Using the sampling tables, select a number of training and qualification records for process operators and employees conducting Q.C. activities related to the sterilization process. Where a process is operated over more than one shift, training records from all shifts should be included within your review. Confirm that all employees are aware of the device defects that may occur as a result of improper performance of their assigned responsibilities. Confirm that employees conducting Q.C. inspections and tests are aware of the defects and errors that may be encountered while

performing their assigned responsibilities. An important linkage to consider at this point is Management Responsibility (820.25 Personnel).

NOTE: Information that must be reported with the Establishment Inspection Report (EIR) includes: 1. The identification of all sterilization processes used by the firm (e.g. Ethylene Oxide, Gamma irradiation, etc.); 2. The identification of the sterilization process covered; 3. The identification of any standard that the firm claims to follow for the process covered (if applicable); 4. The location of the sterilization sites; 5. The division of responsibilities for sterilization services (e.g. contract testing labs, sterilizer, finished device manufacturer, packaging, labeling etc.); 6. The SAL ; and, 7. whether or not parametric release is utilized.

Sampling Plans: Instructions & Tables



Sampling Plan Instructions

Note: Factors to consider when selecting a sampling table and sampling size may include the risk of the device being inspected or the records being sampled, and the amount of time you have allocated to this portion of the inspection.

1. Select the table based upon how sure you want to be about what is observed. For example, if you are reviewing Device History Records of a life supporting device, you may choose to use Table 2 (99% Confidence). You may choose to use Table 1 (95% Confidence) for the review of Device History Records regarding a device with lower risk.

2. Select a sample size. If the population of records to be sampled is small (approximately thirty or less), you may choose to review all of the records.

3. Review the sample of records selected. You can terminate your review of the entire sample if you observe objectionable conditions beyond the number stated in the column header[1]. However, if you do not review all of the records in the sample, you may not report additional information that could be useful in further understanding the potential prevalence of the objectionable condition observed, or you may not recognize whether other objectionable conditions exist.

4. When objectionable conditions are observed based upon samples chosen using these tables, report in the Establishment Inspection Report: (a) the total number of records included in the population from which the sample was chosen; (b) the table used to select your sample; (c) the row used to select your sample; and, (d) the sample size selected[2].

[1] If you choose to terminate your review prior to completing the review of the entire sample, in addition to the information contained in instruction 4, report in the Establishment Inspection Report how many records were reviewed prior to your termination of the review.

[2] The information requested in instruction 4 must be reported whenever an Official Action Indicated (OAI) endorsement is considered. Reporting this information may not be necessary when Voluntary Action or No Action is indicated. However, caution is advised when using this reporting discretion because Voluntary Action Indicated endorsements are sometimes elevated to Official Action Indicated.

NOTE:

A. There are no "acceptable" violations of the Quality System Regulation. All Quality System Regulation violations encountered must be handled appropriately according to current FDA policies and procedures. When using the "1 out of:" and "2 out of:" columns, it does not mean no more than that number of Quality System Regulation violations per the appropriate sample size is acceptable. It will only give you an initial understanding of how prevalent the problem may be.

B. When at all possible, all samples should be chosen at random.

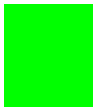


Table 1

Binomial Staged Sampling Plans

Binomial Confidence Levels

Confidence Limit .95≤		0 out of:	1 out of:	2 out of:
A	.30 ucl*	11	17	22
B	.25 ucl	13	20	27
C	.20 ucl	17	26	34
D	.15 ucl	23	35	46
E	.10 ucl	35	52	72
F	.05 ucl	72	115	157

Table 2

Binomial Staged Sampling Plans

Binomial Confidence Levels

Confidence Limit .99≤		0 out of:	1 out of:	2 out of:
A	.30 ucl*	15	22	27
B	.25 ucl	19	27	34
C	.20 ucl	24	34	43
D	.15 ucl	35	47	59
E	.10 ucl	51	73	90
F	.05 ucl	107	161	190

*ucl = Upper Confidence Level

CRC Handbook of Probability and Statistics: Second Edition

Binomial Sampling may be used when trying to make a decision about an endpoint that only has two potential outcomes (e.g., The device history record is compliant or the device history record is noncompliant).

Management Controls Subsystem

Design Controls Subsystem

Corrective and Preventive Actions (CAPA) Subsystem

Medical Device Reporting (CAPA Satellite)

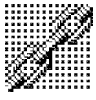
Corrections & Removals (CAPA Satellite)

Medical Device Tracking (CAPA Satellite)

Production and Process Controls (P&PC) Subsystem

Sterilization Process Controls (P&PC Satellite)

Sampling Plan Instructions & Tables



Important Linkages