AdvaMed
Advanced Medical Technology Association

POINTS TO CONSIDER WHEN PREPARING FOR AN FDA INSPECTION UNDER THE QSIT CORRECTIVE AND PREVENTIVE ACTIONS SUBSYSTEM

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Introduction

Background

The Federal Food, Drug, and Cosmetic Act (FD&C Act) requires FDA to conduct biennial Quality System (QS)/Good Manufacturing Practice (GMP) inspections of firms that manufacture class II or class III medical devices, except those that have been exempted from the Quality Systems regulation 21 CFR Part 820. In an attempt to decrease inspection time and increase the focus of medical device inspections, the FDA, in consultation with industry, developed an approach for conducting inspections under the QS regulation called the Quality Systems Inspection Technique (QSIT).

Under QSIT, quality system requirements are divided into subsystems. The FDA, by directing its attention to the subsystems in a firm's quality system, is better able to determine if the firm's quality system is operating in a state of control. QSIT focuses on four of the major subsystems in the QS regulation: management controls, design controls, corrective and preventive actions, and production and process controls. This document discusses only the corrective and preventive actions subsystem.

FDA's August 1999 "Guide to Inspections of Quality Systems" (the QSIT manual) states,

> "The purpose of the corrective and preventive action subsystem is to collect information, analyze information, identify and investigate product and quality issues, and take appropriate and effective corrective and/or preventive action to prevent their recurrence. Verifying or validating corrective and preventive actions, communicating corrective and preventive action activities to responsible people, providing relevant information for management review, and documenting these activities are essential in dealing effectively with product and quality issues, preventing their recurrence, and preventing or minimizing device failures."

To help manufacturers comply with the requirements for corrective and preventive actions (CAPA), AdvaMed has prepared this question and answer document. This document follows the audit process described in FDA's QSIT manual. In addition, two tables are provided (Appendices 5 and 6) that summarize the directions to FDA investigators under the CAPA subsystem of the QSIT manual. Appendix 5 summarizes the procedures that the investigator is asked to review and what should be found in them. Appendix 6 summarizes the records that should be reviewed and what the investigator is asked to focus on.

CAPA Systems

The concept of CAPA is not restricted to the QS regulation or QSIT, but is a widely accepted concept in most quality systems, whether based on GMP, ISO, or some other standard or guideline. Since most modern quality systems strive to improve quality, there must be mechanisms in place to recognize existing or potential quality issues, take the appropriate steps necessary to investigate and resolve those issues, and, finally, make sure the same issues do not recur.

An informal review by the authors of the year 2000 warning letters issued to medical device companies revealed that approximately 15% of the cites (n=813) were concerned with the firm's CAPA system. As evidenced by the significant number of warning letter cites on the topic, firms face many challenges in making the CAPA system work as intended. One of the main objectives of this "Points to Consider" document is to provide firms with a means to assess their current

CAPA system. Although directed toward a QSIT inspection, this document addresses other quality systems inspections or audits, including ISO.

Firms should ensure that their CAPA system looks beyond product issues and considers other quality issues, including problems associated with systems and processes. During failure investigation or root cause analysis, firms will occasionally conclude their investigation when the nonconforming part or material is identified and corrected. However it is important to note that an important element of the CAPA system is to address processes and procedures. In many instances, if a given process were working appropriately, it would be less likely for nonconformities to be introduced into the system. Where practical, processes and procedures should be reviewed and considered as potential root causes for product or quality issues.

CAPA systems are inherently data driven. This means that without adequate, relevant data, it can be difficult to draw definitive conclusions about product or quality issues. There is an increasing reliance on technology to help gather and sort data. One of the challenges facing many firms is the proliferation of small, uncontrolled data repositories within the organization. Departments or individuals now have the ability to create and manage databases that house important quality information that is invisible to the rest of the organization. Where practical, firms should seek out and use tools that allow for the collection of that information in a more centralized manner, while still allowing those same departments and individuals to do their respective jobs. By doing so, the organization has a better chance of recognizing and resolving quality issues. FDA and other agencies recognize the increasing reliance on technology, and are promulgating regulations to address the basic controls necessary to assure the trustworthiness and reliability of electronic records. FDA's regulations addressing these basic controls include 21 CFR Part 11 Electronic Records; Electronic Signatures; and 21 CFR 820.70(i) Automated Processes. According to these rules, software and software changes for all automated systems used as part of the quality system must be validated.

As the quality system within an organization matures, there should be a natural shift in emphasis from corrective action to preventive action. Issues that need to be corrected usually become obvious. However, issues that have the potential for becoming a problem are less readily recognizable. How can a firm sift through all its internal data to find those few situations that might be the precursors of problems down the road? There is no easy answer. Firms will likely turn to technology solutions to address this surveillance activity. In addition, there is increased availability of public information through federal agencies, other government agencies, and industry organizations that provide insight to product issues that may have direct relevance to a firm's products. Companies should consider looking to these external data sources as inputs to their CAPA system.

A good CAPA system should be a "closed loop." This is common terminology, yet it can be difficult to define because of the process variability from firm to firm. In general, "closed loop" refers to at least two elements of the CAPA system. First, it means there are sufficient mechanisms in place to ensure that the CAPA process runs through all the required steps to completion, and that management and those responsible for product quality have visibility and input to the process. In addition, management with executive responsibility must be aware of and review the outputs of the CAPA system. It is very easy for firms to focus on completing the individual tasks of a particular corrective action, yet lose track of the original purpose of the CAPA system. For example, a particular product problem may get resolved, yet no follow-up is ever performed to make sure the documentation was complete or that the resolution was effective. In this example, the loop was never closed.

Second, a good CAPA system "closes the loop" on many of the documented issues by directly providing input into the design control requirements of its quality system. For example, nonconforming product procedures are directed at assuring that the nonconforming product is

identified and corrected prior to distribution or is prevented from being distributed. Frequently, a correction or temporary change will be implemented to assure that the next lot of products does not have the same nonconformity. A good CAPA system will pick up where the correction or temporary change left off, looking for the root cause of the problem and conducting a corrective action in an effort to ensure that the nonconformity doesn't show up in any successive lots of the same or similar products.

References

In compiling this document, we relied principally on the following sources: Federal Food, Drug, and Cosmetic Act; the Quality System/Good Manufacturing Practice Regulation, 21 CFR Part 820; the Preamble to the Quality System Regulation, which provides insight into FDA's interpretation of the regulation (61 FR 52654); Trautman, K.A., *FDA and Worldwide Quality System Requirements Guidebook for Medical Devices*, 1997, Milwaukee, Wisconsin; FDA's August 1999 "Guide to Inspections of Quality Systems"*; *Compliance Program Guidance Manual 7382_845*; ANSI/ISO/ASQ Q9000-2000 – *Quality Management Systems: Fundamentals and Vocabulary*; and other FDA publications available on their web site. See the appendices for additional references and resources.

*NOTE: FDA's August 1999 *Guide to Inspections of Quality Systems* can be accessed at: http://www.fda.gov/ora/inspect_ref/igs/qsit/qsitguide.htm. The *Compliance Program Guidance Manual 7382_845* can be accessed at: http://www.fda.gov/ora/cpgm/default.htm.

Important Information

Please note that manufacturers can comply with the QS regulation requirements in different ways depending on the type of product that the company manufactures, the size of the company and the company culture. The examples included herein are meant to illustrate some of the ways a corrective or preventive action might be performed. A firm may have a different process that is equally effective. **This document is not legal advice or a legal standard**. Companies must ensure that their individual practices and procedures comply with the requirements of 21 CFR Parts 820, 803, 806, and 821, and may wish to obtain legal advice from a qualified attorney on this topic. Contact Nancy Singer, Special Counsel at AdvaMed for more information.

Questions and Answers

Q.1 What might be the elements of a CAPA system that address the requirements of the quality system regulation?

A.1 Elements of a CAPA system addressing 21 CFR 820 might include:

- Definitions of key terms used throughout the CAPA system.
- Procedures for the review and analysis of product and quality data from defined sources in order to identify existing and potential product or other quality issues.
- Procedures for performing investigations on product or other quality issues to determine their causes.
- Procedures to assist in identifying what actions might be taken to correct and prevent the recurrence of product and quality issues and to require that the actions are verified or validated and implemented in a timely manner.
- Procedures for prioritizing, monitoring, and tracking CAPA activities.
- Process flow charts (or other tools) reflecting the inputs and outputs of business processes showing how relevant information on quality issues, as well as corrective and preventive actions, are communicated to management for review and disseminated to those responsible for assuring product quality.
- Procedures which provide links to other operational areas including:
  - Management Responsibility (21 CFR Part 820.20)
  - Quality Audit (21 CFR Part 820.22)
  - Training (21 CFR Part 820.25(b))
  - Design Controls (21 CFR Part 820.30)
  - Purchasing Controls (21 CFR Part 820.50)
  - Production and Process Control (21 CFR Part 820.70(b))
  - Process Validation (21 CFR Part 820.75)
  - Acceptance Activities (21 CFR Part 820.80)
  - Nonconforming Product (21 CFR Part 820.90)
  - Installation (21 CFR Part 820.170)
  - Complaint Files (21 CFR Part 820.198)
  - Servicing (21 CFR Part 820.200)
  - Statistical Techniques (21 CFR Part 820.250)
  - Medical Device Reporting (21 CFR Part 803)
  - Corrections and Removals (21 CFR Part 806)

Q.2 How might a firm define key terms relating to corrective and preventive action?

A.2. Firms may consider defining key terms as follows:

- *Correction* – action to eliminate a detected nonconformity. Corrections typically are one-time fixes, but they may be done in concert with a corrective action if the problem recurs or otherwise persists. See ISO Q9000:2000. A correction is an immediate and sometimes temporary solution while a corrective action may be required to permanently address the issue.

- *Corrective action* – action to eliminate the cause(s) of a detected nonconformity or other undesirable situation. See ISO Q9000:2000. The corrective action should eliminate the recurrence of the issue.
- *Effectiveness evaluation* – documented process to establish that an action was effective and accomplished the objective that was intended.
- *Management review* – process used by the management with executive responsibility of a firm to determine that the quality system is appropriate, suitable, effective and that adequate resources are being applied where needed. See AdvaMed's "Points to Consider When Preparing for an FDA Inspection Under the QSIT Management Controls Subsystem" document. It can be found on the Web at http://www.advamed.org/regulatory/index.shtml. Scroll down to the "*Points to Consider* document issued" on the first page of Regulatory Issues.
- *Nonconforming material* – material that does not meet quality acceptance criteria as defined by a specification or similar document or material that has been determined to be not fit for use. See 21 CFR 820.90.
- *Preventive action* – action to eliminate the cause of a potential nonconformity or other undesirable potential situation. See ISO Q9000:2000. The preventive action should eliminate or prevent the occurrence of the potential issue.
- *Quality audit* – a systematic, independent evaluation to determine whether quality activities and related results comply with written requirements and whether these requirements are implemented effectively and are suitable to achieve the stated objectives. See 21 CFR 820.3(t).
- *Root cause analysis* – the analysis necessary to determine the original or true cause of a system, product, or process nonconformity. This effort extends beyond the effects of a problem to discover its most fundamental cause.
- *Timely* – taking action in a timeframe commensurate with the risk and magnitude of the issue and in a manner that would be taken by a reasonable company that is concerned with protecting the public health.
- *Trend* – a sequence or pattern of data. Analysis of a trend is performed to detect a special cause amidst the random variation of data.

Q.3 What are potential sources of data about product and quality issues?

A.3 Potential sources of data about product and quality issues might include:

- Acceptance activity records relating to component, in process, and finished device testing
- Complaints
- Medical Device Reports (MDRs) and Vigilance Reports
- FDA 483s and Warning Letters
- Reports of system, process or product nonconformities
- Process monitoring data (e.g., statistical control charts, trends, run charts, etc.)
- Calibration and maintenance records
- Scrap, rework and "Use As Is" (UAI) records

- Clinical adverse events
- Internal, external, supplier and third party audits*
- Returned products analysis
- Installation and/or repair reports
- Spare parts usage
- Customer and/or technical service requests
- Field service and/or warranty reports
- Customer feedback (e.g., surveys, polls, etc.)
- Historical records from previous corrections
- Corrective and preventive actions
- Lawsuits and other legal actions
- Published literature
- Reports from employees

*NOTE: In the course of an investigation, an FDA investigator may seek information on how a particular nonconformity was detected. Under some circumstances, this could lead to requests for information relating to internal audits, supplier audits, or management reviews. Firms should develop an internal policy or procedure on how to handle these requests. Internal audits, supplier audits, and management reviews are not typically shared with an FDA investigator.

All of the above examples, with the exception of FDA 483s and Warning Letters, lawsuits, and, published literature, are derived from the firm's quality system, and are defined as "quality records" by FDA. All quality records should be considered a potential source of important system, product, and/or process-related information. Firms should maintain an accurate inventory of data repositories so information can be effectively analyzed. Wherever practical, firms should try to reduce isolated data sources and consolidate or compare data from different sources to improve the likelihood of recognizing existing or potential product or quality issues.

The Quality System regulation provides that the requirement to make records under the Quality System regulation available for inspection and copying by FDA officials does not apply to management reviews, internal audits, and supplier audits (21 CFR 820.180(c)). **However, comment 182 of the preamble to the Quality System regulation provides that FDA may seek production of management reviews and quality audit reports "…in litigation under applicable procedural rules or by inspection warrant where access to the records is authorized by statute."** If quality audits or management reviews are the only mechanism the firm uses to document their corrective and preventive actions, those records may be open for FDA inspection. Firms should not rely on quality audits and management review reports or minutes as the sole documentary evidence of their corrective and preventive actions.

A designated FDA employee under 21 CFR 820.180(c) may request that, under the requirements of the regulations, "management with executive responsibility" certify in writing that management reviews and quality system audits have been performed and documented, the dates on which they were performed, and that "any required corrective action has been undertaken." If an FDA employee makes this request, **seek the assistance of legal counsel before providing this certification.** When providing the

certification concerning whether or not "any required corrective action has been undertaken," counsel should consider including language, "to the best of my knowledge, on the basis of the facts before me, it appears that a good faith effort has been made to ensure that any required corrective action deemed necessary by management has been undertaken."

Q.4 How might a firm demonstrate that data from these sources have been analyzed to identify existing product or quality issues?

A.4 Firms should implement procedures that provide for the periodic analysis and review of product and quality data to identify trends that may indicate action is warranted to correct existing product or quality issues and to develop actions to prevent their recurrence. Information that could lead to corrective actions may come from both internal and external sources as described in Answer 3 (A.3) above. Data that are particularly useful for identifying existing product or quality issues may come from:

- Complaints
- Medical Device Reports and Vigilance Reports
- FDA 483s and Warning Letters
- Reports of system, process or product nonconformities
- Scrap, rework and "Use As Is" records
- Clinical adverse events
- Internal, external, supplier, and third party audits (See NOTE in A.3 above)
- Returned products analysis
- Repair reports
- Field service and/or warranty reports
- Reports from employees

The firm should be able to demonstrate that the data were properly recorded and analyzed according to procedure. If electronic systems are used to capture and analyze this information, the software should be validated. Mechanisms should exist to demonstrate that data from different sources are collectively and comparatively analyzed. Analysis should include looking for outliers, comparing actual results to expected results (including trends or expectations established through design or process validations), and comparing them in relation to established and actual process parameters.

An example of a corrective action is located in Appendix 1.

Q.5 How can a firm demonstrate that product and quality data have been analyzed to identify potential product or quality issues?

A.5 Firms should implement procedures that provide for the periodic analysis and review of product and quality data to identify areas of improvement or preventive actions. Information that could lead to preventive actions may come from both internal and external sources as described in Answer 3 (A.3) above. Preventive actions allow firms to take measures before product becomes nonconforming. Data that are particularly useful for identifying potential product or quality issues include:

- Acceptance activity records relating to component, in-process, and finished device testing
- Process monitoring data (e.g., statistical control charts, trends, run charts, etc.)
- Calibration and maintenance records
- Internal, external, supplier, and third party audits (See NOTE in A.3)
- Customer feedback (e.g., surveys, polls, etc.)

In addition to procedures, firms should be able to demonstrate that the analysis activities actually occurred. See Answer 4 (A.4) above.

An example of a preventive action is located in Appendix 2.

Q.6 How can a firm demonstrate to an FDA investigator that CAPA data are complete, accurate and timely?

A.6 An important aspect of the CAPA system is that the data coming into the system are complete, accurate and timely. Firms should implement procedures that describe:

- What the sources of product and quality data are
- How the data are to be captured
- How the data are to be analyzed, including the method of analysis
- When the data are to be analyzed
- What steps are taken after analysis

Firms should also be able to demonstrate that the activities described above actually occurred. In addition, process flow charts can be an effective tool to describe the process. Significant potential or actual quality problems detected and corrected before they resulted in misbranded or adulterated product reaching the marketplace may demonstrate that a given analysis was timely. Where practical, firms should consider automating certain activities, such as trending reports or other analyses, to run at predetermined time intervals. When validated, automated activities provide one mechanism for ensuring complete, accurate, and timely processes in the CAPA system. Automated activities should be periodically reviewed to ensure they remain relevant and accurate in the current operational environment.

Q.7 What types of statistical methods (where necessary) are appropriate for detecting recurring quality issues?

A.7 Appropriate statistical methods might include:

- Statistical process control (SPC) charts
- Pareto analysis
- Tolerance bound determination
- Linear and non-linear regression analysis
- Experimental design (DOE – Design of Experiments) and analysis of variance

- Product survival analysis of incomplete life data
- Stress-fatigue analysis
- Graphical methods (histograms, scatter plots, etc.)
- Advanced methods (e.g., fitting models to frequency distributions, computing and plotting hazard functions, etc.)

Statistical methods can also be useful when they are applied across different data sources to analyze comparable issues. For example, by comparing manufacturing nonconformances across multiple manufacturing sites, information regarding common suppliers, or complaint information against customer service reports, the firm can achieve a more complete perspective of the entire organization.

Although statistical techniques are powerful tools for analyzing product and quality issues, they should not be the only mechanism used by firms. Non-statistical techniques provide an opportunity to rely on corporate knowledge and expertise to recognize issues sometimes before there is an observable trend. These techniques include:

- Management reviews
- Quality and/or material review boards
- Safety committees (internal or external)
- Employee suggestion programs
- Individual clinical, product or engineering expertise
- Other internal reviews

This type of review often helps to reduce any geographical or departmental bias that may be introduced when identifying issues.

Appendix 3 lists useful references and web sites related to statistical methods.

Q.8 What might be elements of failure investigation procedures?

A.8 Failure investigation procedures might include provisions for:

- Establishing who is responsible for evaluating product or quality issues and determining if a failure investigation is necessary.
- Maintaining a record when no failure investigation is made, including the reason and the name of the individual responsible for the decision.
- Describing how investigations are conducted and what records are maintained.
- Defining the content and format of the failure investigation report.
- Identifying the failure modes.
- Determining the significance and risk of each failure mode.
- Determining the depth to which a failure investigation is to be carried out including when an investigation should include root cause analysis.
- Requiring review and approval of the failure investigation, risk analysis, conclusions and any required actions.

- Feeding information into FMEA (Failure Effects and Modes Analysis) or another risk management tool and tying back to the risk analysis originally performed during the design phase.

A thorough failure investigation needs to take into consideration design, process and labeling deficiencies. "User error" or "use error" should not generally be considered a root cause.

Appendix 4 lists useful references and web sites related to failure investigations.

Q.9 What might be the elements of a thorough failure investigation?

A.9 The comprehensiveness and depth of failure investigations should be commensurate with the magnitude of the issue, and the potential risk the issue presents to the patient and/or end user. Typically, the failure investigation should include:

- *Problem identification and definition* – Once identified, the issue must be characterized and defined in order to understand the potential scope and impact. This characterization should include the documented risk analysis.
- *Investigation* – The issue is investigated and documented, including results of analyses (data, process, operations and/or other sources of information) and identification of failure modes and conclusions regarding root cause(s).
- *Rationale* – If a failure investigation or analysis is not performed, the record should include the reason no investigation was performed and the individual responsible for the decision.
- *Action Plan* – A thorough failure investigation might include information and other data that can be useful in crafting an action plan to address the issue.

Appendix 4 lists useful references and web sites related to failure investigations.

Q.10 What factors might be taken into consideration when determining if a product or quality issue is "significant"?

A.10 Typically, the following factors are taken into consideration in determining if a product or quality issue is significant:

- *Is there potential for user or patient safety issue?* – Likelihood that the issue may result in a death or serious injury, even if the cause is determined to be user error.
- *What is the classification of the device?* – Class II and III products tend to have higher risks associated with them than Class I products.
- *Is there a reliability issue?* – Does the nonconformance or product issue affect the product's reliability?
- *Did the product meet its specifications?* – Does the nonconformance or product issue cause the product to fall outside of established specifications?
- *Was the product labeling involved?* – Does the nonconformance or product issue cause the product to be misbranded, adulterated, or otherwise not properly identified?

- *Has the frequency of occurrence for a known issue changed?* – Is the nonconformance or product issue occurring at a higher rate than expected over a given period?
- *Is the issue difficult to detect?* – A nonconformance or product issue that is difficult to detect is less likely to be identified and corrected prior to causing a problem.

Q.11 What evidence might be shown to an FDA investigator to demonstrate that the CAPA system is functioning as intended?

A.11 Evidence to show an FDA investigator that the CAPA system is functioning properly might include:

- *CAPA inputs* – Sources of product and quality data are routinely reviewed.
- *Analysis* – Documentation demonstrating that data were analyzed for possible unfavorable trends or other indicators of product or quality issues.
- *Investigations* – Documentation demonstrating that qualified personnel have investigated unfavorable trends, nonconformances, and product issues.
- *Action records* – Corrective or preventive action plans and other records demonstrating action start and end dates.
- *Effectiveness checks* – "Before" and "After" product or process quality trend reports or other analyses. These checks should establish that the action effectively prevented the recurrence (or initial occurrence) of the nonconformance.
- *Verification checks* – Engineering change orders (ECOs) or other control forms for initiating a change to a product or process.
- *Validation checks* – Design verification, design validation, and process validation protocols, and summary reports to ensure the actions were effective and that they do not adversely affect the device.
- *Control checks* – Training records, product tracking information, segregation, reprocessing, rework or final product disposition records with appropriate authorizations.
- *Timeliness checks* – Tracking mechanisms to demonstrate that actions are conducted in a timely manner.
- *Management checks* – Management review agendas and schedules, corrective/ preventive action status, aging and closeout reports.

An effective CAPA system should be a "closed-loop" process. There should be mechanisms in place to assure that corrective actions are closed in a timely manner consistent with the type of issue, the corrective action was effective in eliminating the cause(s) of the nonconformance, the action has been reviewed by management with executive responsibility, information has been disseminated to parties responsible for product quality and other people affected by the action, and, if the action is not shown to be effective, an evaluation is performed to determine if a quality issue continues to exist.

Q.12 What evidence might be shown to an FDA investigator to demonstrate that corrective and preventive actions for product and quality issues were implemented and documented?

A.12 Evidence to show an FDA investigator to demonstrate that corrective and preventive actions for product and quality issues were implemented and documented might include:

- Engineering change orders
- Process/product verification and validation records
- Training records
- Corrective or preventive action close-out reports
- Nonconformity close-out reports
- Effectiveness evaluations
- Current trends (or other indicators) that demonstrate actions were effective

Q.13 Do all nonconformities require a risk analysis, failure investigation, and corrective action?

A.13 The preamble to the October 7, 1996 Quality System regulation provides insight into FDA's position on these matters. In comment 159 of the preamble, which relates to the degree of corrective or preventive actions, FDA states "FDA cannot dictate in a regulation the degree of action that should be taken because each circumstance will be different, but FDA does expect the manufacturer to develop procedures for assessing the risk, the actions that need to be taken for different levels of risk, and how to correct or prevent the problem from recurring, depending on that risk assessment." A CAPA system should provide mechanisms to assess risk throughout the process.

Nonconformities should be evaluated as to their potential risk to patients and users. This evaluation should be supported by a documented product risk assessment performed under design controls or subsequently generated at the time the nonconformity is identified. The determination whether or not to pursue failure investigation and/or corrective action is based in part on the magnitude of the problem and any related risk, and should be made by properly trained and qualified individuals. The determination and, if appropriate, the rationale for not pursuing corrective action should be documented in accordance with criteria defined in written procedures.

It is reasonable to assume that there will be nonconformities that have no hazard potential or for which the root cause is unable to be determined or is attributed to purely random circumstance. These conclusions should be well-documented and the rationale explained in a written record. These situations may not require further action, but they should be periodically reviewed and incorporated into the review of trend reports or other analyses to ensure no recurrence or continuing problem exists. When the root cause cannot be determined due to insufficient data, methods to acquire additional data should be considered and incorporated into a formal action plan.

Q.14 What evidence might be shown to an FDA investigator to demonstrate that information regarding nonconforming product and quality issues and corrective and preventive actions have been properly disseminated?

A.14 Evidence to show an FDA investigator that information regarding nonconforming product and quality issues and corrective and preventive actions have been properly disseminated might include:

- Notations in employee* training records for process or procedure changes as the result of a corrective or preventive action.
- Agendas relating to the management review of the quality system including corrective and preventive actions, with dates and attendance lists.
- Internal reports, memos and other communications with employees directly responsible for assuring product quality and the prevention of quality issues.
- Documentation showing that the firm considered the necessity of, or complied with the reporting requirements contained in 21 CFR 803, Medical Device Reporting, and 21 CFR 806, Reports of Corrections and Removals.
- Document and Engineering Change Control records.

*NOTE: The term "employee" refers to permanent, contract, and temporary employees.

Q.15 What evidence might be shown to an FDA investigator to demonstrate that CAPA information is an integral part of the management review process?

A.15 Evidence to show an FDA investigator that CAPA information is an integral part of the management review process might include:

- Procedures for management reviews that contain standard agendas with headings that discuss the review of corrective and preventive actions.
- Agendas relating to the management review of the quality system including corrective and preventive actions, and certification that reviews were conducted.
- Completed or closed corrective and preventive actions* that resulted from the management reviews.
- Schedules of management reviews (past and future).
- CAPA analysis reports submitted for Management Review.

*NOTE: In the course of an investigation, an FDA investigator may seek information on how a particular nonconformity was detected. Under some circumstances, this could lead to requests for information relating to internal audits, supplier audits or management reviews. Firms should develop an internal policy or procedure on how to handle these requests. Internal audits, supplier audits, and management reviews are not typically shared with an FDA investigator.

Q.16 What might be the elements of a Medical Device Reporting (MDR) system that addresses the requirements of 21 CFR Part 803, Medical Device Reporting?

A.16 Elements of an MDR system addressing 21 CFR Part 803 might include:

- Procedures for the timely and effective identification, communication, and investigation of events that may be subject to medical device reporting requirements.
- Procedures that provide a standard mechanism to determine if an event meets the criteria for MDR reporting and that require documentation of the information evaluated and the conclusion drawn.
- Procedures for submitting complete and timely reports to FDA.
- Procedures for maintaining documents and other records related to the evaluation and submission of MDR reports.
- Procedures for maintaining MDR event files and distinguishing them from other complaint records.

Q.17 What evidence might be shown to an FDA investigator to demonstrate that the MDR system is functioning in accordance with 21 CFR Part 803?

A.17 Evidence to show an FDA investigator that the MDR system is functioning in accordance with 21 CFR Part 803 might include:

- MDR files that demonstrate a standard evaluation and review was completed and the submission of MDR reports was done in accordance with written procedures and the requirements of the rule.
- Complaint files for unreported events that demonstrate a standard evaluation and review was completed, who completed the evaluation, and an adequate rationale for not reporting the event.

Not all complaints are reportable under the regulation. The firm should establish written procedures that describe how complaints are analyzed and what criteria are examined to determine if the complaint is reportable. If the firm determines that an apparent device-related death, serious injury, or malfunction is not reportable, the decision must be documented and it must be made by an individual suitably qualified to make a medical judgment (i.e., physician, nurse, risk manager, or biomedical engineer). Because there are time constraints prescribed in this rule, the firm should be able to demonstrate that their process allows for the timely evaluation of complaints.

Q.18 What evidence might be shown to an FDA investigator to demonstrate that the firm's management has implemented the reporting requirements of 21 CFR Part 806, Reports of Corrections and Removals?

A.18 Evidence to show an FDA investigator that the firm's management has implemented the reporting requirements of 21 CFR Part 806 might include:

- Written procedures for the evaluation of corrections and removals to determine if they must be reported to FDA under the rule.

- Files of reportable removals or corrections that show the firm submitted complete, written reports to the appropriate FDA District Office within 10 working days of initiating the action.
- Files demonstrating that unreported removals or corrections have been processed through the firm's CAPA system, contain the required information, and all such actions have been reviewed and evaluated in accordance with written procedures. A written rationale why the removal or correction was not reportable under the rule should be maintained.

Q.19 What evidence might be shown to an FDA investigator to demonstrate that a firm that manufactures trackable products has the capability to meet the requirements of 21 CFR Part 821, Medical Device Tracking Requirements?

A.19 Evidence to show an FDA investigator to demonstrate that a firm manufacturing trackable products has the capability to meet the requirements of 21 CFR Part 821 might include:

- Written procedures that describe the processes used for the collection, maintenance, and auditing of tracking data.
- Examples of tracking records that indicate all the FDA-required elements are present.
- If the firm is required to track devices under the rule, they will have received written notification of this by FDA. This communication should be available to an investigator.
- Audit schedules* and procedures that show audits being conducted in accordance with the rule, including:
  - Audits of the adequacy of device tracking practices
  - Audits of the accuracy and completeness of tracking data
  - Audits scheduled at the frequency required by FDA

*NOTE: FDA's policy relative to review of quality audit results is stated in "Compliance Program Guidance" (CPG) Manual 7151.02 (CPG Manual Sub Chapter 130.300). This policy prohibits FDA access to a firm's quality audit results during a routine inspection or investigation. However, the FDA reserves the right to these records in limited circumstances as described in the CPG. This manual is posted on the Web at http://www.fda.gov/ora/cpgm/default.htm.

Appendix 1
Corrective Action – Example

Background: Company X manufactures portable Bone Growth Stimulator devices that operate with a rechargeable Ni-Cad battery. A supplier provides the batteries to Company X, which packages the batteries with the Bone Growth Stimulator. The rechargeable battery has component specifications for battery longevity based upon typical treatment protocols found in the "Instructions for Use for the Bone Growth Stimulator" manual.

Issue : Analysis of complaint data by the Quality Department at Company X identified a significant increase in the number of reports of short battery life.

CAPA Review: The Quality Department immediately evaluated this category of complaint and determined that there was a low risk of potential injury to the patient. The battery performance issue was brought before the CAPA Committee. The Committee concurred with the Quality Department's risk assessment and an investigation was initiated. The action was assigned to the Quality Engineer.

Failure Investigation: The Quality Engineer was able to obtain several of the batteries involved in the complaints. Analysis of the batteries revealed that they did not achieve the specified capacity levels. The batteries and investigative results were forwarded to the supplier for further analysis.

The Quality Engineer held a preliminary meeting with the Purchasing Department and other Quality Department representatives to review purchasing controls and incoming materials receiving procedures to determine the root cause of how these batteries made it through the process and into finished devices.

Supplier Investigation and Action: The supplier confirmed the analysis of the batteries. The supplier's investigation determined that the reduced life was the result of defective raw materials used in three different lots. The supplier provided replacement batteries for the lot numbers in question, and agreed to implement improved incoming acceptance procedures and sampling methods that would detect defective raw materials. The Quality Department and the supplier jointly developed an improved process for assessing the incoming quality of the batteries.

Action Plan: Company X contacted customers and sent replacement batteries for all products using the nonconforming batteries. Inventory and Work-In-Progress (WIP) product was purged of nonconforming batteries. Based upon written procedures, Company X determined that this action was not reportable to the FDA under 21 CFR Part 806. The Quality Department devised a special report to monitor complaints of decreased battery life to be used over the next 12 months to verify that the corrective action was effective. The Purchasing Department created a plan to improve their process for selecting and qualifying raw materials, to monitor similar situations, and to prevent this type of problem from reccurring in the future. The supplier provided reports over the next three months to verify that their inspection program was adequate to identify nonconforming raw materials and finished batteries before they were shipped to Company X. The corrective action resolution was reviewed by the CAPA Committee and closed at a subsequent meeting.

Management Review: At the next regularly scheduled management review, management with executive responsibility reviewed the corrective actions taken since the previous meeting.

Appendix 2

Preventive Action – Example

Background: Company Y manufactures surgical sutures of varying materials and diameters. Sutures are individually packaged in small packets. The individual packets are labeled with the type of suture material and the diameter, and a color indicator strip that is designed to help the user easily recognize that the proper diameter has been selected.

Improvement Opportunity: While calling on several accounts, a new Sales Representative noticed that if a variety of suture packets were placed on a procedure tray, it was sometimes difficult to differentiate between the various diameter sutures using only the color strip indicator found on the individual package. The Sales Representative suggested to the Marketing Department that by improving the indicator, selection of the desired diameter suture could be made easier for the medical staff.

CAPA Review: The Marketing Department forwarded the suggestion for improvement, citing possible decreased risk of use error as part of the rationale. The CAPA committee approved an investigation request and assigned it to the Packaging Manager.

Investigation: The Packaging Manager reviewed competitive products and other similar products to gather ideas. Past complaints and returns were reviewed to assess if there may be an ongoing problem with product identification. The Manager then consulted with a Human Factors Engineer to determine if a change to the packaging was warranted. The parties concluded that providing more than one visual indicator of suture size could optimize usability.

Action Plan: Several options were discussed with the Graphic Artist. A concept was developed to improve the color strip indicator by printing the suture size (diameter) in a repetitive manner along the indicator strip. The user would then have two visual methods to distinguish the diameter during a procedure. The Graphic Artist created a new print plate and produced a limited number of prototype suture packages. The Marketing Department conducted a survey of medical professionals to assess their preference. All those surveyed felt the new packages improved usability and decreased the likelihood of use error.

Since the proposed modification would require a change in the product packaging, the Packaging Manager took the opportunity to review other outstanding product labeling issues. In concert with the Regulatory Affairs Department, a new label was designed to cover not only the proposed change, but to address some minor layout changes submitted by the Marketing Department.

Management Review: The Packaging Manager presented the findings to the Management Review Board. The Board decided to proceed with the change by phasing out existing packaging. Regulatory Affairs was notified to ensure the appropriate notifications of labeling change were made to regulatory agencies.

Appendix 3
Statistical Methods

Useful References:

1) Statistical Methods for Quality Improvement, Kume, Hitoshi (editor), 1987, ISBN 4-906224-34-2. 231 pages
2) Quality Engineering Statistics, Dovich, Robert A., 1992, ISBN 0-87389-141-4
3) Introduction to Statistical Quality Control, 4th Edition, Montgomery, Douglas C., 2001, ISBN 0-471-31648-2. 816 pages.
4) ISO/TR 10017:1999, "Guidance on Statistical Techniques for ISO 9001:1994."
5) Juran's Quality Control Handbook, J.M. Juran and Frank Gryna (eds.), 4th Edition, 1988, ISBN 0-07-033176-6.

Useful Web Sites:

1) CDRH: http://www.fda.gov/cdrh
2) American Society for Quality: http://www.asq.org
3) AdvaMed: http://www.advamed.org
4) NIST/SEMATECH Engineering Statistics Handbook: http://www.itl.nist.gov/div898/handbook

Appendix 4
Failure Investigations and Analysis

Useful References:

1) Failure Mode and Effect Analysis: FMEA from Theory to Execution, Stamatis, D.H., 1995, ISBN: 0-87389-300-X. 494 pages.
2) The Basics of FMEA, McDermott , Robin, 1996, ISBN: 0527763209. 76 pages.
3) The Root Cause Analysis Handbook: A Simplified Approach to Identifying, Correcting, and Reporting Workplace Errors, Ammerman, M., 1998, ISBN: 0527763268. 144 pages.
4) Root Cause Analysis Handbook: A Guide to Effective Incident Investigation,1999, ISBN: 0865876584.
5) "ISO 14971 Medical Devices" – Application of risk management to medical devices. (This document can be found at https://www.aami.org/secure/marketplace/search.cfm. Enter 14971 as a Keyword and search. Scroll down to ISO 14971:2000. Click on the box beside the title if you want detailed information and purchase price.)
6) Root Cause Analysis: A Tool for Total Quality Management, 1993, ISBN: 0-87389-163-5.

Useful Web Sites:

1) CDRH: http://www.fda.gov/cdrh
2) American Society for Quality: http://www.asq.org
3) AdvaMed: http://www.advamed.org/

Appendix 5
CAPA Procedure Review

The following table is a summary of the instructions provi ded to investigators in the "Guide to Inspections of Quality Systems" (QSIT Manual). This table specifically addresses the procedures investigators are asked to review.

PROCEDURE TO REVIEW	WHAT TO LOOK FOR
CAPA System Procedure(s)	- Definitions of key terms. (If not in procedure, ask management for their interpretation) - How all elements of CAPA required in QS Regulation are carried out: - Method to input product or quality problems into CAPA system - Use of data sources including (at least) acceptance activities, processes, concessions, complaints, service and installation activities, returned products, quality audits, and lawsuits - Requirements for analyzing data using appropriate statistical and non-statistical techniques - Requirements for analyzing data by comparing problems and trends across different data sources - Procedures for failure investigation including identifying failure modes, determining significance of failure modes, decision mechanism for whether to do a failure analysis, depth of failure analysis - Identification of action(s) needed to correct problems and prevent recurrence - Requirements for verification or validation to ensure effectiveness of action(s) and absence of adverse effects - Requirements for implementation and documentation of changes - Mechanism to disseminate CAPA information 1) to those directly responsible for product quality and prevention of problems and 2) to management for review - Mechanism for determining when action is necessary for an identified trend indicating a problem. (If not in procedure, ask management to describe)
MDR Procedure(s)	- If system assures: - Timely and effective identification, communication, and evaluation of events that may be mdr–reportable - A standard review process to determine when an event meets mdr reporting criteria - Timely transmission of complete mdrs to fda - Documentation of what information was evaluated to determine if an event was reportable - Safekeeping of all reports submitted to fda - Access to information that facilitates timely follow-up and inspection by FDA

PROCEDURE TO REVIEW	WHAT TO LOOK FOR
Tracking Procedure(s)	- If firm is aware of requirements to: - Notify FDA if it goes out of business and provide copies of tracking records to FDA - Transfer tracking records to firm purchasing its tracked devices - Continue tracking devices it stops manufacturing or importing if it remains in business - If system addresses the capability to: - Identify location and other required data for devices undistributed to patients within 3 working days after request by FDA - Identify location and other required data for devices distributed to patients within 10 working days after request by FDA - If procedure(s) addresses remaining requirements of 21 CFR Part 821.25(a-c) for collection, maintenance, and auditing of tracking data
Audit Procedure(s)	- If procedure(s) addresses: - Functioning of tracking system - Accuracy and completeness of data in tracking system

Appendix 6
CAPA Records Review

The following table is a summary of the instructions provided to investigators in the "Guide to Inspections of Quality Systems" (QSIT Manual). This table specifically addresses the records investigators are asked to review.

NUMBER OF RECORDS TO REVIEW	WHAT TO REVIEW	WHAT TO LOOK FOR
CAPA System Records		
Use sampling tables	Records from one or two quality data sources	- If reviewed data were entered into CAPA system - If data entered are complete, accurate, and entered in a timely manner
No number specified	Historical records that may show unfavorable trends (e.g., trending data, corrective actions, acceptance activities)	- If preventive actions have been taken regarding unfavorable trends (e.g., product and quality improvements or use of statistical process control techniques) - If data from in-conformance product are analyzed to detect shifts - If statistical process control techniques are being used where applicable
Use sampling tables	Failure investigation records for more than one failure mode (if possible)	- If failure investigation procedure is being followed - If all reviewed failure modes are captured in data summaries (e.g., reports, charts, spreadsheets, etc) - If depth of investigation is sufficient to determine the corrective action necessary
One record	Significant failure investigation that resulted in a corrective action	- If root cause was identified so that verification or validation could be accomplished
Use sampling tables	Incomplete failure investigations	- Potential unresolved product nonconformances - Potential distribution of nonconforming product
Use sampling tables	Records of nonconforming product for which corrective or preventive action was not taken	- Potential distribution of nonconforming product
Use sampling tables	Concessions made for nonconforming product	- If concessions were appropriate to product risk - If quality system requirements were followed - If concessions were made solely to fulfill marketing needs

Use sampling tables	Significant corrective actions (e.g., a product or process change to correct a problem)	- If the change(s) could have extended beyond the action taken. If so, ask for rationale for not extending the action beyond that taken. - If the actions were effective: - Look at subsequent trend results for similar problems - See if change was verified or validated to ensure effectiveness and absence of adverse effects
Use sampling tables	Most recent corrective or preventive actions	- If they have been documented and implemented - If information related to problems was disseminated to individuals directly responsible for assuring product quality and prevention of problems
One record	Recent CAPA event	- What records were submitted for management review (Note: review raw data given to management, not results of management review)
MDR System Records		
Use sampling tables	MDR event files	- If MDR event files are prominently identified and easy to access - If MDR event files contain: - information that describes a device-related death, serious injury, or malfunction - evaluation of information including decision to submit or not to submit an MDR - copies or references to supporting documentation - MDR reports (including any follow-ups), baseline reports, and MDR-related correspondence, as appropriate
Use sampling tables	MDR reports submitted to FDA	- If written procedures were followed (e.g., with respect to timely reporting, complete investigation, consistency, etc.)
Use sampling tables	Complaints not reported as MDRs and records from one additional source of quality data (e.g., service reports, repair reports, returned goods files, etc.)	- If they contain information relating to MDR-reportable events. If so, ask for rationale for not submitting MDR reports.
Reports of Corrections and Removals Records		
Use sampling tables	Corrections or removals that have been reported to FDA	- If correction or removal was reported to FDA within 10* days of its initiation - If FDA was provided with all information required by 21 CFR Part 806.10 *NOTE: The QSIT Manual does not include the word "working" between 10 and days. FDA regulation 21 CFR 806.10(b) states "10 working days".
Use sampling tables	CAPA files	- If CAPA files reveal apparent Class I or II recalls that were not reported to FDA

Use sampling tables	Corrections or removals that did not need to be reported to FDA per 21 CFR Part 806.20	- If all information required by 806.20 is present - If information is retained for 2 years longer than the expected life of the device involved - If these files reveal apparent Class I or II recalls - If any claims for exemption from the reporting requirements of 806 are well-founded - If device was sold to another firm, confirm these files were transferred to new manufacturer or importer
Medical Device Tracking Records		
No number specified	Prior manufacturer's tracking records (if applicable)	- Existence and maintenance of prior manufacturer's tracking records or equivalent information
One or two records	Tracking files containing information requested by FDA	- If required information was provided in required timeframe(s)
Based on length of time tracking has been a requirement for the firm	Audit schedules	- Audits of tracking system every six months for first three years and annually thereafter