U.S. Food and Drug Administration
Implantable Devices that Contain Batteries Critical to Quality Inspection Pilot
IMPLEMENTATION REPORT

Table of Contents

1 Introduction

1.1 Purpose

The purpose of this report is to describe the results of the Case for Quality Inspection Pilot program. The pilot established a collaborative framework for determining specific operations, design considerations, and controls that impact the quality and safety of implantable devices that contain batteries. Post-inspection feedback, gathered from both firms and FDA, was analyzed to determine the effectiveness of the program. These results provide an opportunity for FDA and industry to gauge any changes in inspectional outcomes as a result of focusing inspections on activities critical to product and process quality.

1.2 Summary of Methodology

The Focus on Quality (FoQ) team, operating under the Case for Quality initiative, worked with the FDA Center for Devices and Radiological Health's (CDRH) Battery Working Group to develop a summary of factors, failure modes, and design considerations that are critical to device quality for implantable devices that contain batteries. This information was discussed with industry experts and their feedback was used to ensure that the information was current and relevant to factors impacting the quality of these devices.

The FoQ team drafted a document based on the critical to quality information with the intent of ensuring the investigator had the most current critical details regarding the safety and effectiveness of implantable devices that contain batteries. Registered establishments who manufacture devices of this type were identified and senior personnel from these establishments were contacted to ask whether they would be willing to participate in an inspection where investigators had been prepped with "critical to quality information." The relevant district offices were also contacted to ensure investigational personnel understood the purpose of the pilot and how it was to be conducted within the scope of the Quality System Inspectional Technique (QSIT). Both establishments and investigators were made aware that participation in the pilot included responding to a post-inspection interview. This report summarizes the information gathered in those interviews.

1.3 Overview

In internal interviews conducted by the FoQ team, 48% of participating Office of Regulatory Affairs (ORA) employees responded that FDA could improve device quality by improving its approach and tools for inspections to better focus on quality areas. Half of those employees thought FDA could use an increased risk-based approach to do so. Interviews of CDRH Office of Compliance (OC) staff revealed that 55% of participating staff felt that the Agency's inspectional and compliance focus could be changed in order to influence better device quality.

Data provided in the *Understanding Barriers to Quality*[1] document indicates an industry perception that much of the Agency's regulatory focus is on production and process control and nonconforming products. Industry also perceives that many of the critical quality risks for devices reside in product/process design and post-production activities.

This pilot focused on elements that are critical to quality for implantable devices that contain batteries to better inform inspections, to engage the manufacturer and FDA in quality discussions, and to focus resources on both sides to quickly correct issues and improve quality operations. Focusing on implantable devices that contain batteries narrowed the scope of the pilot to one type of component that cuts across device product categories. Batteries that are incorporated into implantable devices are also an area in which CDRH has developed a good technical foundation.

ORA and OC developed an inspectional approach that focuses on specific operations, design considerations, and controls. The pilot utilized the current QSIT inspectional model, the Quality System Regulation. The resulting Critical to Quality document, which included quality indicators for implantable devices that contain batteries, was shared with manufacturers and investigators prior to inspections. This allowed the firms to devote resources to activities that would impact the parameters identified in the document and the investigators to prepare specifically for the device or component at hand.

1.4 Glossary

- CDRH — Center for Devices and Radiological Health
- CDT — Comparative Data Transparency Sub-Initiative
- CfQ — Case for Quality Initiative
- CtQ — Critical to Quality
- DMQ — CDRH Division of Manufacturing and Quality
- FoQ — Focus on Quality Sub-Initiative
- OC — CDRH Office of Compliance
- ORA — Office of Regulatory Affairs
- SE — Stakeholder Engagement Sub-Initiative

[1] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDRH/CDRHReports/ucm277272.htm

2 Description of Evaluation

The FoQ team sent an invitation for a one-hour teleconference interview to the primary firm contact, typically the Quality Vice President, at companies where a CtQ inspection had been conducted. FDA encouraged the firm to invite any additional firm representatives to provide feedback at the interview. All questions for the interview were provided to the firm prior to the teleconference with FDA. The questions involved the firm's feedback on engagement with the investigator, resource utilization, focus on quality versus compliance, and recommendations for change. In the last part of the interview, the firm provided ratings for statements made about their satisfaction with different areas of the inspection on a scale from 1 to 5 (with 1 being strongly disagree and 5 being strongly agree). The questions were first read by the FDA participants, and then the firm provided their feedback as the FDA recorded their comments. FDA asked additional follow-up questions as necessary.

Concurrently, a second series of one-hour teleconference interviews were held with the district office investigators who performed the CtQ inspections. When multiple investigators were involved, individual or group interviews were arranged based on their schedules. All of the questions on the survey were provided to the investigators prior to the interview. The series of questions requested the investigator's feedback on engagement with the firm, resource utilization, focus on quality versus compliance, and recommendations for change. In the last part of the interview, the investigator provided ratings for statements made about their satisfaction with different areas of the inspection on a scale from 1 to 5 (with 1 being strongly disagree and 5 being strongly agree). The questions were first read by the FoQ participants, and then the investigators provided their feedback as FoQ recorded their comments. Again, FoQ asked additional follow-up questions as necessary.

3 Results and Analysis

3.1 Firm Responses

Overall, the responses from the firms were positive. They believed that the CtQ pilot inspections promoted interactions with FDA, improved the clarity of the expectations, increased their satisfaction with engagement, and focused the inspection towards quality. However, the firms believed that it did not change discussions with management throughout the inspection or any internal practices.

There were mixed responses on whether the CtQ inspections were different from regular QSIT inspections and on the utilization of resources and the involvement of additional groups within the company. Some firms felt that the CtQ pilot forced additional resources and groups to be involved, while others saw no change.

FDA issued one firm a FDA-483. However, FDA did not issue inspectional observations related to the CtQ indicators to any of the firms. Therefore, the firms could not comment on the 483 prioritization scheme.

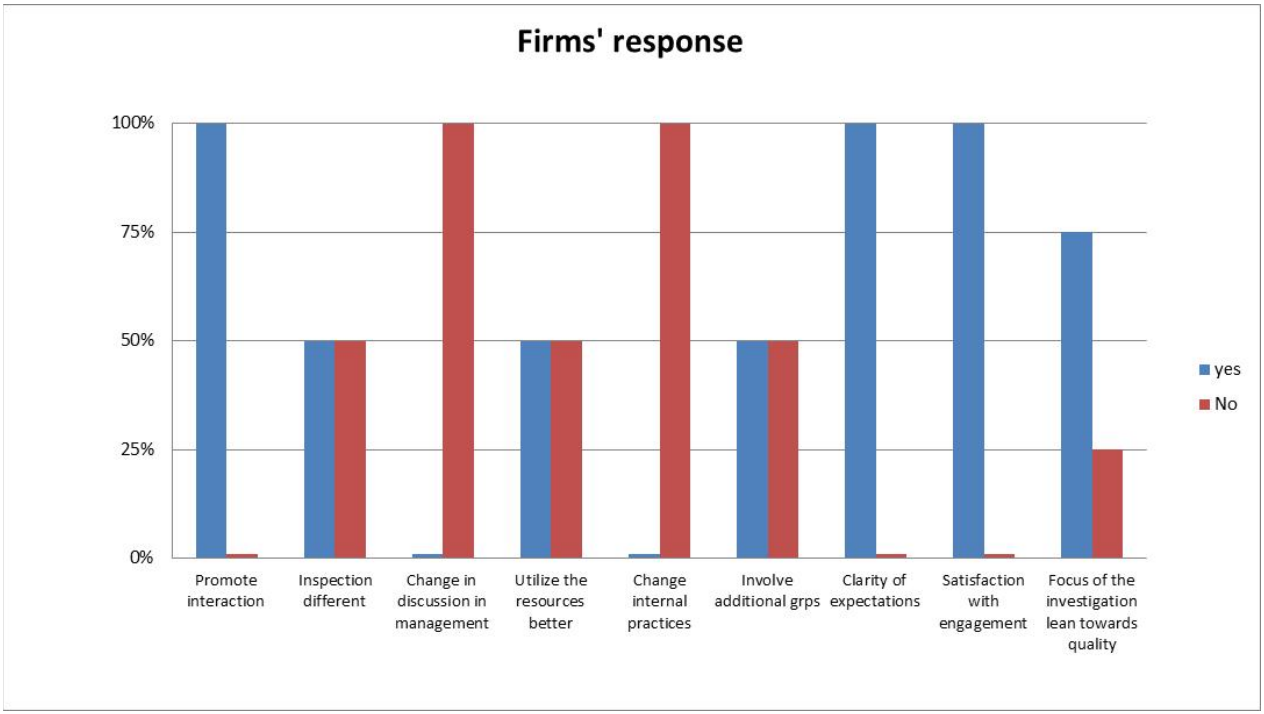

Figure 1. Graph of firms' responses to FoQ survey

3.2 Investigator Responses

Overall, the responses from the investigators were positive. They believed that the CtQ pilot inspections promoted interaction with the firms, helped the discussion with the management, increased their satisfaction with engagement, and focused the investigation towards quality.

50% of the investigators thought that the CtQ pilot required more time to prepare for the inspection. 60% of the investigators thought that the pilot did not change the amount of time/resource utilization during the inspection or the time for pre-inspection preparation. 50% of the investigators said that the CtQ inspections were the same as QSIT inspections except that the CtQ document aided the inspection.

FDA issued one firm a FDA-483. However, FDA did not issue inspectional observations related to the CtQ indicators to any of the firms. Therefore, the investigators could not comment on the 483 prioritization scheme.

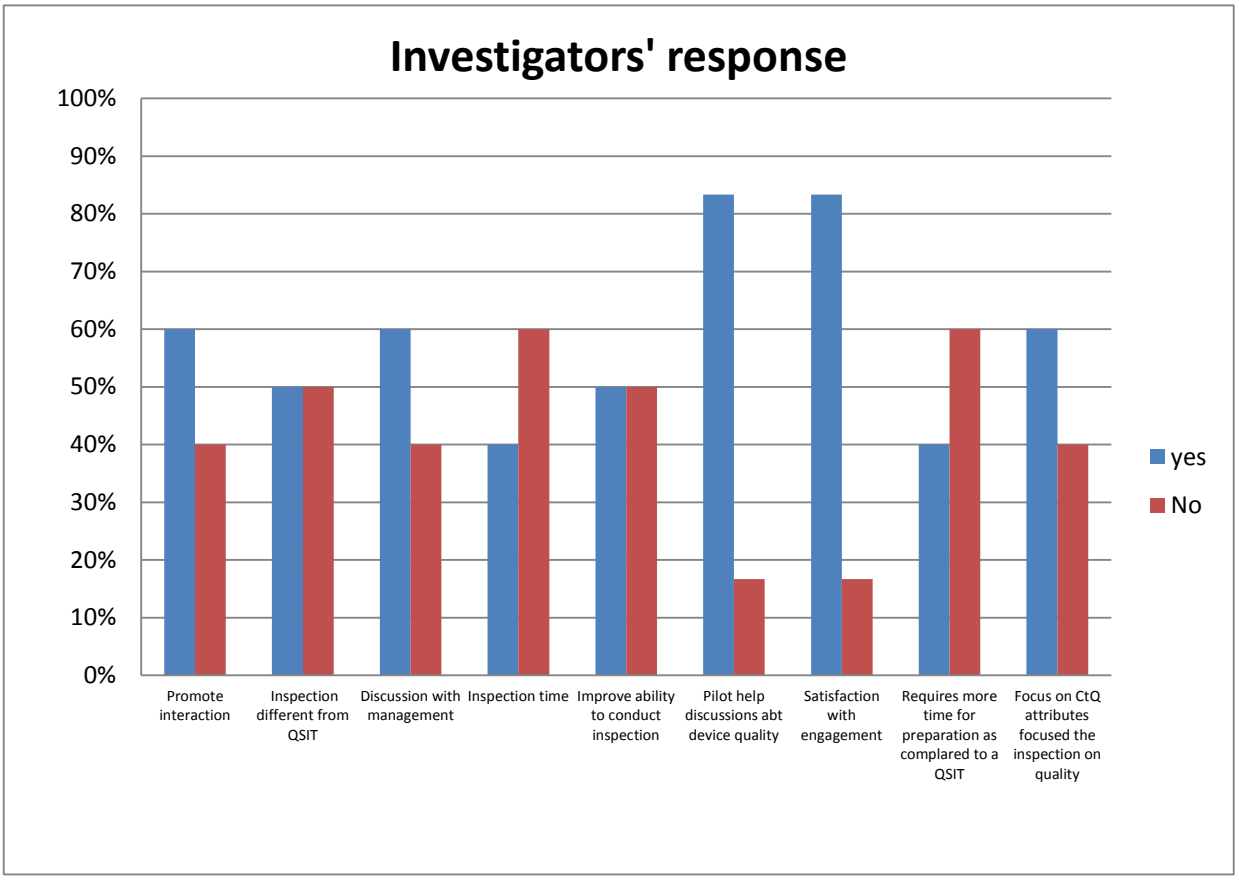

Figure 2. Graph of investigators' responses to survey

3.3 Analysis

Focus on Quality

Overall, the CtQs did appear to provide a better exchange regarding quality between the inspectors and the firms. According to firm feedback, “it does drive quality before inspection” and focuses on “technical aspects rather than procedural aspects.” One firm stated that the inspection content “looked more at the approach to the quality of the device” and “focused on more important aspects of Quality System vs typos and missteps” by looking at “systems and critical aspects of device and systems” and “what’s important to ensure quality of devices.” Some firms believed that the addition of CtQ to QSIT made discussions more focused on CtQ but “at a cost,” including increased preparation time and more resources needed.

District Investigators either saw improvement or potential for improvement with the CtQ method. One investigator stated that the firm “gave me their opinion about what is important to the quality of their device.” Investigators found themselves looking at more technical aspects during the inspection, with one noting “there was more engagement on batteries and how it is incorporated into the overall device. I looked a lot more at the battery and supplier – including longevity studies for a 6 year life cycle. I would not have seen these in a normal QSIT inspection.” Another investigator thought that a risk-based approach was an improvement, saying “I tried to focus on the risk to the patient. Because of the focused background information, it improved my ability to conduct the inspection.” Another investigator appreciated the guidance as an initiation point to the inspection method, “For other complex devices, it might take one or two days to just start. It takes time to figure out quality indicators.” Some investigators did not see as much improvement but realized that they were able to “have a number of robust discussions” with this method and “focus on issues that had more impact.” For them, the scope of the inspection may have played a role. For example, one investigator pointed out that their Battery CtQ inspection was held at a firm that does not use a rechargeable battery, so the inspection method would have been a better tool at a firm manufacturing that kind of battery design.

Resource Utilization

In terms of resource utilization, some firms appreciated the targeted approach. One firm stated that “it helps because we are looking at the important elements vs. entire group of elements.” They felt they were able to prepare, having access to “the test before you take it.” One firm felt that there was not much difference and was surprised that the inspection did not take longer and the topics were covered quickly. Another firm felt the CtQ approach was more burdensome because there was a more technical discussion. That firm stated that “unless FDA deemphasizes something else, this does take more time and consumes more technical resources to get deeper into the design. Probably the investigator would have finished two days earlier by our estimate.”

Preparation Time

Most investigators felt that preparation for the CtQ inspection took more time, however they also noted that the extra work resulted in more confidence and efficiency in the inspection. One investigator stated that they "prepared with more specificity" and used the assignment to "pinpoint where to go" and they found that "if there were issues they had an idea of if it was significant or not." Some investigators suggested that the method was optimal for newer investigators since "it gives them something to focus on and a tool to understand the technology." However, it was noted that the document was technically challenging so "a background aimed for novices would be good for investigators." Overall, investigators felt that the inspections at the firms either took the same amount of time or less time. One investigator stated that the inspection did not necessarily take more time, but it forced them to cover topics that they normally would not have. In their case the topics were extraneous, since "there were no real issues with the battery, so coverage of the battery was just done to complete the pilot program." One investigator communicated their concern that the pilot program may seem biased since the firm was provided all the questions in advance so they were able to prepare. The investigator felt that during future inspections, if CDRH does not provide CtQ indicators to a firm in advance, time would not be saved because the firm would not be prepared to handle the questions.

Changes in Quality Practices

Overall, the firms were in consensus that they did not see too much change to their practices based on the CtQ inspection process. One firm stated that "we already know the criticality regardless of an FDA audit or not," while another indicated that they had already implemented many of the practices that were the focus of the inspection, but it "was helpful to see FDA's viewpoint on these matters, which identified some opportunities to improve." One firm stated that the inspection changed their preparation for the inspection rather than their practice; they "brought out engineering notebooks vs. compliance structured documents." Firms were confident in their current practices; one firm stated, "we always had a strong focus on risk and the areas of our product and process that we believe is the most important. But we can see benefit to a company that does not have this approach."

Industry and FDA Engagement

Results from the interviews appear to indicate that both firms and investigators appreciated the increased opportunity for engagement, which resulted in improved discussions between the two parties. "The interaction and engagement with the FDA investigation was much more interactive. The dialogue was open and positive. There was explaining and asking of questions." Additionally, there was positive feedback regarding the mutual understanding of CtQ indicators and their importance, as opposed to strict compliance regulations. "Yes! There was a better use of time on more important elements versus strictly compliance items." Investigators observed a difference in how firms responded to CtQ questions, instead of regulation based questions. "[The firm] appreciated the quality approach versus compliance with regulations. The firm opened

up more and was more cooperative…items were explained more thoroughly. They gave their opinion on the quality indicators of the device. It was a two-way conversation."

FDA-483 Prioritization

FDA issued one firm a FDA-483. However, FDA did not issue inspectional observations related to the CtQ indicators to any of the firms. Therefore, investigators could not comment on the 483 prioritization scheme.

Transparency

Many of the firms and investigators described positive opinions of transparency to the firms by providing what would be evaluated. The firms appreciated the efficiency that the transparent nature of the CtQ pilot allowed them. One firm stated, "Getting the information ahead of time allowed [us] to get the information together and identify the best people to have available. No warning would have taken more time." This also allowed industry to have a greater understanding of the questions and inquiries from the investigators, thus improving the dialogue between both parties. "The firm is able to know where the questions are coming from and can address them better, instead of having no idea of where an investigator is coming up with a question. This also enables the firm to address the question better because they can have the resources available."

In addition, the firms found they were able to dedicate effort to proactively assessing and improving the areas identified as Critical to Quality. The investigators also had positive feedback regarding transparency on what was covered regarding CtQ. "Management was ready for the CtQ inspection since they were involved in the assignment. They had binders with documents, procedures, etc. that they anticipated [we] would ask for." One firm stated that they have always been focused on risk and product processes and that the CtQ inspection reinforced the importance of these activities. "[In preparation for the inspection, our firm] was able to go over the information and give it a second look instead of focusing on completing an assignment. This allowed [us] to take two steps back." Alternatively, an investigator stated that one firm may have "gone overboard with their preparations" for CtQ and were not prepared for unexpected questions regarding follow-up to three complaints, as their focus for inspection preparation revolved mostly around CtQ indicators.

Firms that have adequately considered device quality will likely be open to discussing CtQ with the FDA investigator. An investigator discussed her experience regarding the openness of the firm and their device quality. "We were able to have frank discussions with the firm concerning device quality. They were already on board and discussions were frank and open." However, if the firm has not considered CtQ elements when developing and manufacturing their device, they may not be as open and forthcoming during discussions. One investigator stated that "Industry is happy to share information on what they are doing well", but the investigator mentioned that when the firms are not doing well, they focus on justifying their actions. He concluded, "The level of engagement needs to be open and honest, that will be challenging."

4 Conclusion

The goal of this pilot was to assess how the agency and industry can engage on quality using existing compliance tools and regulations. To achieve this goal, the pilot evaluated an alternative inspection engagement by focusing the inspection on what is deemed Critical to Quality. Feedback from firms and investigators provided insight into outcomes such as inspection efficiency, resource utilization, open dialogue, engagement, transparency, and overall device quality. Opinions trended favorably from both firms and investigators towards continuing the CtQ inspections and further expanding the scope by creating CtQs for more devices. Various recommendations for improvement were given, including providing easier to read technical guidances to investigators and improving the scope of inspections so that firms are inspected for technologies that are directly applicable to the firm's specific device. The Division of Manufacturing and Quality (DMQ) in the Office of Compliance is currently developing additional Critical to Quality Information documents and procedures and policies for distribution to investigators prior to inspections and publishing them for industry access.

APPENDIX A: Implementation Report Approval

The undersigned acknowledge that they have reviewed the ***Case for Quality Inspection Pilot Implementation Report*** and agree with the information presented within this document. Changes to this **Project Implementation Report** will be coordinated with, and approved by, the undersigned, or their designated representatives.

Signature: _____ Date: _____

Print Name: _____

_____

Title: _____

Role: Project Manager

APPENDIX B: References

The following table summarizes the documents referenced in this document.

Document Name	Description	Location
FDA Investigations Operations Manual	*The IOM is the primary guidance document on FDA inspection policy and procedures for field investigators and inspectors.*	*http://www.fda.gov/ICECI/Inspections/IOM/default.htm*
Compliance Program Guidance Manual 7382.845	*FDA's Compliance Programs provide instructions to FDA personnel for conducting activities to evaluate industry compliance with the Federal Food, Drug, and Cosmetic Act and other laws administered by FDA.*	*http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/ComplianceActivities/ucm248922.htm*
GHTF/SG3/N19:2012	Nonconformity Grading System for Regulatory Purposes and Information Exchange	

APPENDIX C: Battery CtQ Industry Engagement Questions

Questions for Consultants

1. For primary lithium batteries, what are the top three underlying causes of premature battery failure that you have observed?
2. For primary lithium batteries, which cell chemistries have you observed to be the most likely to cause high internal resistance over time, and how might high internal resistance be avoided?
3. For lithium ion rechargeable batteries, what are the top three underlying causes of premature battery failure that you have observed?
4. For lithium ion rechargeable batteries, what is the number one cause of internal battery shorts?
5. If a battery manufacturer asked you to come up with one critical-to-quality attribute for primary lithium and one critical-to-quality attribute for lithium ion rechargeable batteries, what would these be?

Questions for Battery Manufacturers

1. For lithium primary cell and lithium ion rechargeable batteries, which are the three most critical factors related to design to prevent premature battery failure?
2. For primary lithium and rechargeable lithium ion batteries, what are the three most important design verification tests to ensure batteries will operate for their intended use over the stated lifetime of the battery?
3. What are the top three factors in minimizing resistance increase over the life of the cell?
4. For rechargeable lithium-ion batteries, what are the three most important factors to consider to minimize lithium plating?
5. For lithium primary cell and lithium ion rechargeable batteries, which are the three most critical factors related to manufacturing to prevent premature battery failure?

Questions for Device Manufacturers (Implantable Devices With Batteries and Non-Implants)

1. What are the three most critical factors you consider when choosing a battery for your firm's devices?

2. What are the three most critical factors that you consider when choosing a supplier of batteries?

3. When devices are returned alleging battery problems (premature depletion or leakage), what do you consider to be the three most important failure analysis steps to be taken?

4. What top three factors do you consider to be most critical-to-quality for battery-powered implantable medical devices, and how does your firm ensure those critical-to-quality attributes are met?

5. What has been the biggest "lesson learned" that came as a result of battery failure that you have used to improve either your firm's device or the battery in the device?

APPENDIX D: Implantable Battery Critical to Quality Indicators

A. Introduction to batteries used in implantable devices

Batteries used in implantable devices can be primary cell (non-rechargeable) or rechargeable. The three primary functional components of a battery are the negative electrode, positive electrode, and the electrolyte.

Lithium batteries are a common type of primary cell battery. Lithium batteries have lithium metal or lithium compounds as an anode. These are commonly used in pacemakers, pulse generators, infusion pumps, and implantable cardioverter defibrillators.

Lithium-ion batteries are a common type of rechargeable battery used in implantable devices. The negative electrode of a conventional lithium-ion cell is made from carbon. The positive electrode is a metal oxide, and the electrolyte is a lithium salt in an organic solvent. The electrochemical roles of the electrodes change between anode and cathode, depending on the direction of current flow through the cell. Lithium-ion batteries are commonly used in implantable neurostimulators and deep-brain stimulators.

During discharge in a lithium-ion battery, lithium ions Li+ carry the current from the negative to the positive electrode, through the non-aqueous electrolyte and separator diaphragm. During charging, an external electrical power source (the charging circuit) applies an over-voltage (a higher voltage but of the same polarity) than that produced by the battery, forcing the current to pass in the reverse direction. The lithium ions then migrate from the positive to the negative electrode, where they become embedded in the porous electrode material in a process known as intercalation. Diffusion-Induced Stress (DIS) can result in electrode failure in the form of fracture due to intercalation and phase transformation during charge/discharge.

Organic solvents easily decompose on anodes during charging. However, when appropriate organic solvents are used as the electrolyte, the solvent decomposes on initial charging and forms a solid layer called the solid electrolyte interphase (SEI), which is electrically insulating, yet provides sufficient ionic conductivity. The interphase prevents decomposition of the electrolyte after the second charge. Failure to form a good SEI layer results in accelerated aging, degradation and failure.

Risks associated with failures of devices such as infusion pumps, pacemakers, pulse generators, and implantable cardioverter defibrillators include premature explant of the device and failure to deliver therapy (which can result in patient death).

B. QSIT Corrective and Preventive Actions Subsystem

Battery-related issues with implantable devices often result in premature explant of the device. Symptoms of battery-related problems with implanted devices can include premature elective replacement indicators, failure to deliver therapy, inability to charge a rechargeable

device, and increased recharge burden for a rechargeable device. Failure analysis of explanted devices with battery-related issues may reveal premature battery depletion below the low voltage threshold for recharging (re-chargeable batteries), battery leakage, high internal resistance (primary cell batteries), internal battery shorts, and separator shut-down. Investigations should be conducted to ascertain the underlying cause of the device failure, where possible [21 CFR 820.100(a)(2); 21 CFR 820.198(c)].

Evidence of battery-related problems with implantable devices can be found in quality system data sources other than complaints. These include, but are not limited to: failures during receiving, in-process, and finished device acceptance activities [21 CFR 820.80], failure to meet acceptance criteria during design verification [21 CFR 820.30(f)], and failure to meet acceptance criteria during validation of the processes used to manufacture the batteries [21 CFR 820.75(a)].

The manufacturer must collect, analyze, and act on quality data related to appropriate indicators and parameters [21 CFR 820.100(a)]. Quality data from complaints and non-conforming products, as well as information from design verification and process validation, can give indications that there are battery-related problems with the devices. If there appear to be indications of actual or potential quality problems related to the battery, the electrical circuit associated with the battery, or other aspects of the device, these quality problems should be traced to the underlying cause in the design of the battery or device, and/or the manufacturing of the battery or device, and appropriate corrective actions taken.

C. **QSIT Design Controls Subsystem – Critical to Quality Indicators**

Host device design issues:

1. The essential design outputs of the device must be identified. These essential design outputs include design features that are critical to quality for the device. [21 CFR 820.30(d); Design Controls subsystem, Design Controls subsystem, QSIT objective #5]

2. The manufacturer must assess the impact of purchased products and services, including purchased batteries and outsourced battery-related design, on the essential design outputs. For suppliers that provide products or services related to the essential design outputs of the device, the degree of purchasing controls must be commensurate with the risk of the supplied product or service. [21 CFR 820.30(d), 820.30(g), 820.50; Design Controls subsystem, QSIT objective #5]

3. During the development of specifications for the device and device components, potential effects of tolerance stacking must be considered where appropriate. For example, will a battery lid at the maximum end of a width dimension reliably weld to a battery can at the minimum end of a width dimension? Where appropriate, the effects of tolerance stacking should be verified. [21 CFR 820.30(d), 820.30(f); Design Controls subsystem, QSIT objectives #5 and 7]

4. The manufacturer must design the device to prevent contamination of the electronics inside the device. The device must be hermetically-sealed to prevent bodily fluid intrusion into the device, which can corrode the electronics. Appropriate methods of providing hermetic seals must be considered during the device design. The adequacy of the hermetic seals must be verified during the design of the device. [21 CFR 820.30(c), 820.30(d), 820.30(f), Design Controls subsystem, QSIT objectives #4, 5, 6, 7]

5. The device should be designed to mitigate battery issues, including abnormal charging (forced and reversed charging, charging for too long a duration), and over-temperature, over-voltage, and over-current conditions for the battery. Most devices contain overcharge protection mechanisms, often as a part of the device software; however, occasionally a design or manufacturing defect can cause a bypass of these mechanisms and result in overcharge failures. These controls (or protections) can be implemented in the battery and/or the host device. [21 CFR 820.30(f), 820.30(g); Design Controls subsystem, QSIT objectives #5 and 8]

6. The manufacturer should design mechanisms for retrieving information on the implantable device from outside the patient. Important considerations include accuracy of data, distance of programmer from the implantable pulse generator, and security of the communications. [21 CFR 820.30(g); Design Controls subsystem, QSIT objective #8]

7. Design changes must be verified or validated before implementation. In particular, changes involving the battery management circuit for the device (due to component obsolescence, for example) must be thoroughly understood and verified prior to implementing the change. [21 CFR 820.30(i); Design Controls subsystem, QSIT objective #13]

Battery design issues:

1. If the battery is designed and/or manufactured by a supplier, thorough and comprehensive battery specifications and quality requirements must be understood and agreed upon by the battery supplier and medical device manufacturer. [21 CFR 820.30(d); Design Controls subsystem, QSIT objective #5; 21 CFR 820.50; Production and Process Controls subsystem, QSIT objective #2]

2. The electrical requirements of the device under its reasonably foreseen operating conditions must be defined and understood when making a selection as to the battery. For example, the device might draw low amounts of current continuously to maintain the device settings, draw a moderate amount (milliamps) of current intermittently if the device has a radiofrequency telemetry function, and an infrequent but high current (amps) draw if performing defibrillation. The battery selected must be capable of providing power to meet the electrical requirements

of the device over the expected lifetime of the device. [21 CFR 820.30(c), 820.30(d); Design Controls subsystem, QSIT objectives #4 and 5]

3. Reliability, as determined per the approved design inputs, must be verified. This can include, but is not limited to, techniques such as developing prediction models, electrical stress analysis, and exploratory testing (e.g. Highly Accelerated Life Test or HALT). [21 CFR 820.30(f), Design Controls subsystem, QSIT objectives #7]

4. If a lithium ion rechargeable battery depletes below a certain voltage, the copper ions from the electrode de-plate. If this occurs and the battery is recharged, the battery can overheat and/or result in battery separator shut-down. Implantable devices using rechargeable batteries should have a low voltage cut-off designed in the electrical circuit or other appropriate mechanism to prevent overheating and/or battery separator shut-down when recharged. [21 CFR 820.30(c), 820.30(d); Design Controls subsystem, QSIT objective #4 and 5]

5. It is known that certain types of battery chemistries, such as the lithium silver vanadium oxide batteries, may generate an abnormally high internal resistance two to three years after implantation, particularly when used in devices that draw low to moderate (milliamp) current continuously or intermittently. This high resistance will result in a safety alert (ERI flag) and lead to premature explant of the device. If using chemistries that are prone to developing high internal resistance in the middle of expected device life, the battery should be designed to avoid this premature failure of the battery due to abnormally high internal resistance. [21 CFR 820.30(d); Design Controls subsystem, QSIT objective #5]

6. Lithium plating (deposition) on the anode surface during recharging (particularly during overcharge conditions) of lithium ion batteries may lead to irreversible capacity loss, short circuits and uncontrolled energetic chemical reactions. Lithium plating can be minimized by optimizing the amount of carbon in the negative electrode and employing proper manufacturing controls on the manufacturing of the anode and cathode subassembly. The battery should be designed to mitigate lithium plating on the anode. [21 CFR 820.30(d); Design Controls subsystem, QSIT objective #5]

7. Abnormal charging (forced, reversed, high charge levels, continuous low rate charging). Charging the battery with voltage beyond the designed upper cell voltage can cause lithium plating and short-circuit of the battery. Most batteries contain overcharge protection mechanisms, however occasionally a design or manufacturing defect can cause a bypass of these mechanisms and result in overcharge failures. The overcharge protection mechanism should have been verified. [21 CFR 820.30(f); Design Controls subsystem, QSIT objective #7]

8. If the service life of the battery is several years, accelerated life testing of the battery including extreme use at or near battery end of life, must be performed to support reliability claims. However, the manufacturer should also be advised to start collecting real-time battery longevity data, since FDA/CDRH/ODE usually requires at least three years of data to support a battery longevity claim of 9 or 10 years. [21 CFR 820.30(g); Design Controls subsystem, QSIT objective #8]

D. **Production and Process Controls subsystem; Purchasing Controls - Critical to Quality Indicators**

1. Manufacturing environmental conditions must be met.

   Batteries must not experience elevated temperatures, low and high pressure, poor ventilation, or elevated levels of moisture. High temperatures can cause increased reaction rates within the battery. This can cause a positive temperature feedback within the battery, causing higher temperatures and eventual thermal runaway. Low temperatures can cause reduced reaction rates in the battery. This can make it more difficult for the lithium ions to insert into the intercalation spaces (for rechargeable batteries), which can result in reduced power and lithium plating of the anode with irreversible capacity loss. Elevated levels of moisture in the manufacturing of the cathode can cause the generation of hydrofluoric acid in the battery, which can cause stress corrosion cracking and battery leakage. [21 CFR 820.50, 820.70; Production and Process Controls subsystem, QSIT objective #2]

2. Manufacturing defects must be avoided.

   Defects include defective cell raw materials or electrode coatings, contaminants introduced during assembly, and misplaced, misapplied, or damaged components. Thermal runaway events can be caused by electrode damage, burrs on electrode tabs, weld splatter from cell tab attachment points, wrinkles or kinks in windings or tabs, and electrode misalignment. [21 CFR 820.50, 820.70; Production and Process Controls subsystem, QSIT objective #2]

3. Processes must be adequately validated.

   Batteries are manufactured using welding processes for the battery can side seam weld, the weld of the battery lid to the battery can, and welding the electrode tabs. The process of welding the battery lid to the battery can is often performed by laser welding. The alignment of the battery lid to can must be tightly controlled, and very small offsets, as well as the effects of tolerance stacking, can lead to a non-robust weld. The materials to be welded are also a consideration. For example, stainless steel is easier to weld than titanium. If different grades of the same material, such as different grades of titanium, are used for the battery lid and can, this may cause an unpredictable weld melt. [21 CFR 820.50, 820.75; Production and Process Controls subsystem, QSIT objective #4]

The device must be hermetically sealed to prevent bodily fluid intrusion into the device, which can corrode the electronics. The processes for creating the hermetic seals must be validated. [21 CFR 820.75; Production and Process Controls subsystem, QSIT objective #4]

4. Process controls must be established to ensure conformance to specifications. This includes material controls, tooling management, and preventive maintenance controls. The device manufacturer is responsible for ensuring that processes (including manufacturing components and subassemblies) performed by suppliers are performed under the appropriate process controls. [21 CFR 820.70; 820.50, Production and Process Controls subsystem, QSIT objective #2]

5. Mechanical stresses must be avoided.

   The battery must not be crushed, impacted, shocked, vibrated, dropped, or penetrated. These abuses may lead to shorting between cell electrodes, localized cell heating which propagates to the entire cell and initiates thermal runaway. [21 CFR 820.130, 820.140, 820.150; Production and Process Controls subsystem, QSIT objective #2]

6. Suppliers must be evaluated based on their ability to provide products and services that meet specified requirements, including quality requirements. These include suppliers of batteries, battery-related design, and outsourced manufacturing processes. The degree of supplier evaluation and monitoring should be based on the risk the supplied product or service poses to the proper functioning of the finished device and the essential design outputs. Supplier evaluation should consider whether the supplier has proven technologies and track record for providing the product or service, the necessary process controls and equipment (e.g. weld tooling fixtures, defined preventive maintenance programs, inspection and testing equipment, the appropriate degree of environmental controls), and understands the quality requirements for the supplied product. [21 CFR 820.50; Production and Process Controls subsystem, QSIT objective #1, 2, and 4]

APPENDIX E: Prioritizing FDA-483 Observations

Preface

This document is derived from work performed by Study Group 3 of the Global Harmonization Task Force (GHTF), a voluntary group of representatives from medical device regulatory authorities and the regulated industry. The basis for this document is "Nonconformity Grading System for Regulatory Purposes and Information Exchange," Study Group 3 Final Document GHTF/SG3/N19:2012.

Introduction

This document is intended for FDA investigators, supervisors, and compliance officers. It introduces a standardized FDA-483 grading system for the purpose of prioritizing FDA-483 observations, giving consideration to whether the observation has direct or indirect impact on product, and whether the observation has impact on factors of the device that are critical to quality.

Scope

This document provides a method to present outcomes of FDA medical device inspections that can be used by FDA investigators and compliance officers for the purpose of presenting a prioritized FDA-483 to inspected firms. The scope of this document is limited to observations regarding medical devices. In situations where an inspection also covers additional commodities (e.g. drugs) in addition to medical devices, the grading system should be used only for those observations related to medical devices and medical device regulatory requirements.

General

The following sections introduce a standardized FDA-483 observation grading system for regulatory purposes. To enable consistent grading, guidance has been provided on how to write an observation.

Writing Observations

Inspections should be performed in accordance with Compliance Program 7382.845 "Inspection of Medical Device Manufacturers" and other applicable assignments and regulatory references. The output of inspections may include FDA-483 observations.

In order for the significance of observations to be characterized utilizing the FDA-483 observation grading system described in this document, it is essential that (1) observations are clearly worded with factual and precise language that enables the reader to comprehend the actual non-fulfillment that was detected during the inspection; and (2) the correct section of the regulation is cited. The information presented should be an accurate representation of the reviewed records, samples and procedures, as well as interviews conducted.

The observation should:

a) be a statement of nonconformity written in a clear, concise manner:

- be self-explanatory and related to the issue, not just be a restatement of the inspectional evidence, or be used in lieu of inspectional evidence

b) be supported by objective evidence:
- justify the extent of evidence (e.g. number of records) - what exactly was found or not found, with an example(s)
- identify the location or basis (source document) for the evidence (e.g. in a record, procedure, interview, or visual observation)

c) identify the specific requirements which have not been met:
- identify the correct section of the regulation, then select the correct corresponding Turbo citation

Multiple instances of non-fulfillment of a regulatory requirement should be combined into a single observation unless the instances originate or relate to different aspects of the regulation(s).

Grading of Observations
The grading of an FDA-483 observation consists of a two-step approach that leads to calculation of a final grade for each observation (Figure 1 – shaded area), followed by the recording of the observations on the FDA-483:

Step 1 – Determine initial grade using the FDA-483 Observation Grading Matrix
Step 2 – Determine final grade by applying additional escalation rules
Step 3 – Record observations in order on the FDA-483 from highest to lowest grade

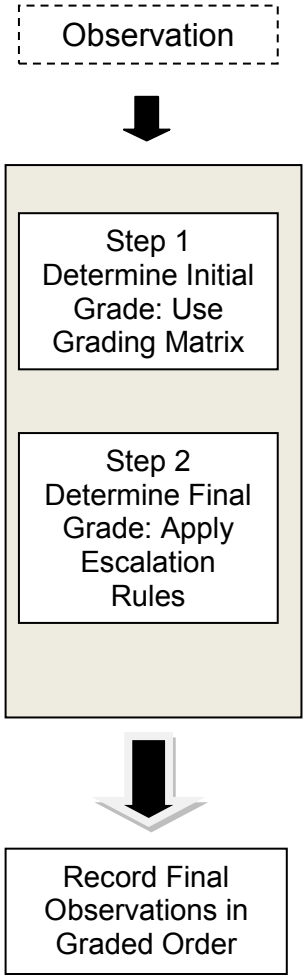

Figure 1: Grading Overview

Step 1: Determine Initial Grade by Using the Grading Matrix

As illustrated in Figure 1 above, using the Grading Matrix is the first step in determining the grade for an observation.

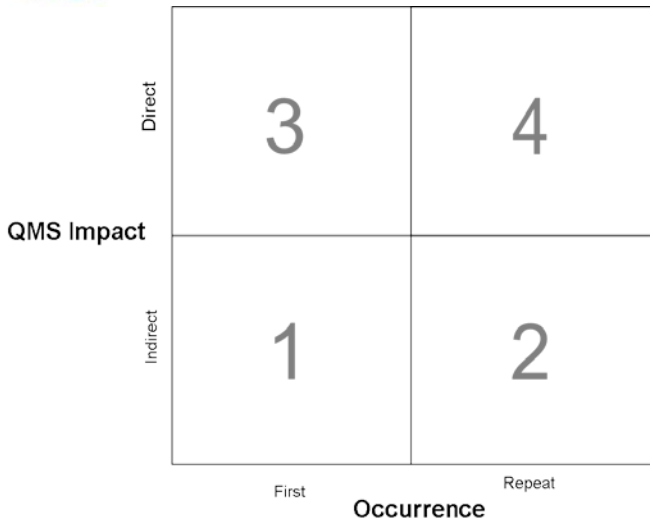

Figure 2: **Grading Matrix**

The Y-axis of the Grading Matrix (Figure 2) is Quality Management System (**QMS) Impact.** It is related to the influence of the FDA Quality System Regulation and other regulations, such as 21 CFR 803 and 21 CFR 806, on medical device safety and performance. It is vitally important to highlight that all the sections of the Quality System Regulation and 21 CFR 806, as well as pertinent sections of 21 CFR 803 are equally required if applicable, to effectively establish and maintain a quality management system that will meet regulatory requirements.

For the purpose of improved stratification in the grading system, the regulations pertaining to medical devices are divided into two categories:

- **Indirect QMS Impact**: 21 CFR 820.20, 820.22, 820.25, 820.40, 820.180, and 820.186 are seen as supporting processes (making it possible or feasible) for the QMS processes to operate. These sections of 21 CFR 820 are therefore considered to have indirect influence on medical device safety and performance.
- **Direct QMS impact:** 21 CFR 820.30, and 820.50 through 820.250 (excluding 820.180 and 820.186), as well as 21 CFR 803 and 21 CFR 806, are seen as having direct influence on design, and manufacturing controls. These are therefore considered to have direct influence on medical device safety and performance.

There are three basic principles that the investigators should follow when writing the observation for purposes of utilizing this grading system:

- When the observation has the potential to affect device safety, performance, and other aspects determined to be critical to quality, it should be written against the specific requirement in 21 CFR 820 found in 21 CFR 820.30, and 820.50 through 820.250, because it has direct QMS impact.

- In addition to observations related to 21 CFR 820.20, 820.22, 820.25, and 820.40, when the observation is against the manufacturer's self-imposed requirements, is not specifically required in 21 CFR 820, 21 CFR 803, or 21 CFR 806; and does not impact safety or performance, then the observation has indirect QMS impact. For example, a manufacturer's procedure for a process revalidation of an injection molding process requires annual revalidation regardless of changes or process deviations. The annual revalidation was not performed, however there were no changes or process deviations noted. In this example, 21 CFR 820.75 does not require annual revalidation. There were no process changes or deviations and there does not appear to be a safety issue. This observation should be considered to have indirect QMS impact.

- Observations can often be written against more than one section of applicable medical device regulations. Therefore, it is the investigator's obligation to determine the impact of the observation on the QMS and assign the appropriate citation in Turbo. The QMS impact of the observation will determine whether the resulting observation will be **Direct** or **Indirect**.

The X-axis of the Grading Matrix in Figure 2 is **Occurrence** and is divided into two categories:

- **First:** The first category addresses an observation in a particular section of FDA regulations identified for the first time. The first time is defined as not observed in the two previous FDA inspections which evaluated the same section of the regulation (e.g. 21 CFR 820.100(a); 21 CFR 820.30(d).

- **Repeat:** The second category is an observation that has been identified within either of two previous FDA inspections which evaluated the same section of the regulation. Such an observation poses an increased risk because it is an indicator that a corrective action has not been adequately taken or implemented.

The "two previous FDA inspections which evaluated the same section of the regulations" was selected because:

- investigators are expected to verify corrections to FDA-483 observations from the previous inspection;
- in order to assess the risk of repeat occurrence accurately, it is important to assess comparable observations;
- historical data beyond the two previous FDA inspections may not represent the current state; and;
- to maintain harmonization between this document and the document "Nonconformity Grading System for Regulatory Purposes and Information Exchange," Study Group 3 Final Document GHTF/SG3/N19:2012.

It is important to ensure that the inspections reviewed for the **Occurrence** assessment, have at a minimum evaluated the same sections of the regulations.

Occurrence in this document is directed at the frequency of an observation cited from one FDA inspection to the next. It is not the occurrences of examples within a given sample size that the investigator may review to determine if an observation exists during an inspection.

Summary of Step 1 – Determining the Initial Grade Using the Observation Grading Matrix

A. Direct or Indirect QMS Impact: When an observation is written and the citation in Turbo assigned, identify whether it is "direct QMS impact" (score of 3) or "indirect QMS impact" (score of 1), as defined above.

B. First/Repeat Occurrence: The investigator should consult the previous two FDA inspection reports which evaluated the same section of the regulations to see if an observation that is identified in the current inspection was previously cited. The observation does not have to be identical to the observation in the previous inspection, just cited to the same section of the regulation (e.g. 21 CFR 820.100(a); 21 CFR 820.198(c)). If the observation is a repeat, the grade increases by 1. For example, a repeat instance of an observation that has direct impact receives a grade of "4." Likewise, a repeat instance of an observation that has indirect impact receives a grade of "2."

Step 2 Determine Final Grade by Appling Escalation Rules
The resultant grading from Step 1 is carried forward to Step 2, which is a rules-based escalation process to address areas of higher risk that have a potential to affect product safety, performance, or aspects identified as critical to quality. Under this grading system, the Step 1 grade is increased by 1 for each rule:

1. Absence of a documented process or procedure required by FDA regulations
The absence of a documented process or procedure will fundamentally affect consistency and effective implementation of any process.

It is critical that the lack of the required procedure or process be obvious within the observation in order to consistently grade the observation.

2. Release of a Nonconforming Medical Device
An observation related to a QMS process that resulted in the release of a nonconforming medical device to the market is direct evidence of a QMS failure. This rule in the grading system is assessing the observation at a higher risk, because nonconforming product is on the market and outside the control of the manufacturer's QMS. If a nonconforming medical device is released under concession with adequate technical and scientific justification, then the nonconformity has been resolved. It is no longer considered a nonconforming product and the escalation rule will not be applied

3. Critical to Quality
Observations related to requirements that have been identified as critical to quality (i.e. related to the essential design outputs or processes that have been identified as critical for the device to meet its safety and performance requirements), the grade increases by 1.

Summary of Step 2 – Determining the Final Grade by Applying the Escalation Rules

In this step of grading, 1 point is added to the initial grade determined in Step 1 for each rule that applies, therefore creating a maximum score of 7.

Rule 1 - Absence: Absence of a documented process or procedure required by FDA regulations, the grade increases by 1.

Rule 2 - Medical Device: Release of a nonconforming medical device outside of the controls of the manufacturer's QMS, the grade increases by 1.

Rule 3 – **Critical to Quality:** Observations related to requirements that have been identified as critical to quality (i.e. related to the essential design outputs or processes that have been identified as critical for the device to meet its safety and performance requirements), the grade increases by 1.

The final grade for an observation under this grading scheme will be a number between 1 and 7. However, the grade of "5" was determined to be the maximum, because (1) this represents a significantly high enough risk that some intervention is required; and (2) a maximum grade of "5" maintains harmonization between this document and document "Nonconformity Grading System for Regulatory Purposes and Information Exchange", Study Group 3 Final Document GHTF/SG3/N19:2012. The observation grade should be identified in the "Supporting Evidence and Relevance" section of the EIR with a bracket after the Turbo citation language and immediately preceding the discussion of the relevance of the observation, with a maximum grade of "5" (e.g. Procedures for corrective and preventive action have not been established. Specifically, Corrective action XYZ, which was closed on X date, does not contain verification of the effectiveness of the actions taken. Supporting Evidence and Relevance [5]…).

For example, an observation that receives a score of "7" will be recorded as a "5" in the "Relevance" section of the EIR. The differentiation between 5, 6, and 7 will be reflected in the order of the observations on the FDA-483. Observations that score to a grade of "7" should be listed on the FDA-483 first, followed by observations that received sequentially lower grades.

In situations where the investigator has either: (1) graded one or more observation(s) as a "5"; or (2) has graded more than two observations as a "4", a full narrative establishment inspection report should be prepared per the Investigations Operations Manual (IOM), section 5.10.4 - NARRATIVE REPORT in order to allow the FDA District Office and/or CDRH Compliance to appropriately classify the inspection and consider which administrative and/or regulatory action to initiate, if applicable.

APPENDIX F: Investigator Survey Questions

The following questions pertain to an inspection that was recently conducted by you under the Critical to Quality pilot. The following questions will help facilitate a discussion so that we can evaluate this pilot inspectional approach:

1. Please indicate whether you feel that the CtQ pilot promoted more interaction/engagement with the firm.
    a. Did it promote more interaction/engagement with the firm?
    b. Was the inspection conducted differently from the normal QSIT approach? How?
    c. Was there a change in the discussion with management due to this approach?

2. Please indicate whether you feel that during the inspection, the CtQ pilot allows for better resource utilization in terms of:
    a. Time for investigator to prepare for the inspection (more or less compared to QSIT approach?)
    b. Was there a difference in the preparation required?
    c. Time to conduct the inspection i.e.: Inspection duration

3. Please describe how the CtQ pilot impacted your interaction with the firm on matters related to device quality and Quality System Regulation (QSReg) compliance.

4. Please indicate whether the pilot inhibited or improved your ability to conduct an inspection and evaluate the firm's compliance with the QSReg while utilizing QSIT.

5. Please provide your assessment of whether the CtQ pilot enabled you to have frank discussions with the firm concerning device quality.

6. If you were king/queen for a day, what changes would you make to the CtQ approach?

Please use the following criteria to indicate whether you agree or disagree with the statements below:

(1) Strongly Disagree
(2) Disagree
(3) Neutral
(4) Agree
(5) Strongly Agree

7. Satisfaction with engagement – as an investigator I was better able to engage in discussions about the quality of the inspected products with the firm.

8. Extent of preparation – preparation for the inspection under the CtQ pilot did not require significantly more time than a Level 2 comprehensive inspection.

9. Communication of findings – it was straightforward to communicate the findings of the inspection to the firm and indicate the extent to which these findings impacted the critical to quality attributes for their devices.

10. Focus of investigation – the focus on critical to quality attributes made the inspection more focused on quality

APPENDIX G: Firm Survey Questions

The following questions pertain to the inspection that was recently conducted by an FDA Investigator at your facility. The following questions are intended to facilitate a discussion to help evaluate this pilot inspectional approach:

1. Please indicate whether you feel that the CtQ inspectional pilot promoted more open conversation with the FDA investigator regarding quality.

    a. Did it promote more interaction/engagement with the FDA investigator?
    b. Was the inspection conducted differently from the normal QSIT approach? How?
    c. Was there a change in the investigator's discussion with management due to this approach?

2. Please indicate whether you feel that during the inspection, the CtQ inspectional pilot allowed for better resource utilization in terms of cost, FTE utilization.

3. Please indicate whether you found that the questions related to CtQ information focused more on your approach to ensuring device quality as opposed to your approach to ensuring compliance.

    a. Did the CtQ pilot lead you to change any of your internal practices?
    b. Did this approach involve additional groups in discussions?

4. Please describe whether an inspection utilizing the CtQ information will impact your firm's approach to corrective actions in response to 483 observations.

    a. Please comment on the clarity of findings
    b. Time to correction of observations

5. Please provide any suggestions or feedback you have regarding the CtQ inspectional approach.

Please use the following criteria to indicate whether you agree or disagree with the statements below:

(1) Strongly Disagree
(2) Disagree
(3) Neutral
(4) Agree
(5) Strongly Agree

6. Clarity of expectations – our firm was clear on the expectations for this inspection at the close of the inspection

7. Satisfaction with engagement – our firm was better able to engage in discussions about the quality of the inspected products with the investigator

8. Clarity of findings – our firm is clear on the impact of inspection findings on device quality

9. Focus of investigation – the focus on critical to quality attributes made the inspection more focused on quality