Lessons Learned in Resolving FDA Warning Letters

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Abstract

Lessons Learned in Resolving FDA Warning Letters

In this presentation, Mark Neal, VP Global Quality Systems and Assurance at St. Jude Medical, will describe his experience and lessons learned from numerous FDA inspections and specifically his work to clear five Warning Letters in four FDA Districts. He will describe how regulatory action is escalated from routine or directed inspections to FDA 483 observations to Warning Letters and the impact of Warning Letters on the business for product approval submissions, design change submission and geography expansion. Mark will share the high level process for responding to the FDA 483 observations and subsequent Warning Letter (if issued) and will describe the approach to clearing the Warning Letter for specific commitments in the Warning Letter response and the criticality of the re-inspection preparation. Lessons learned from these experiences will be shared at each stage. In conclusion, Mark will explain how compliance and quality can be leveraged as a competitive advantage by preventing these types of issues.

Biography

Mark Neal is Vice President of Global Quality Systems and Assurance for St. Jude Medical. Mark has more than 32 years of experience in all aspects of Quality and regulatory compliance. He has broad experience in FDA and ISO Registrar/Notified Body interface including FDA inspections, ISO audits, Warning Letter clearance and product regulatory submissions strategy. Mark has experience in Class I, II and III medical devices, 510(k) and PMA submissions, and with clinical trial requirements. His career has been predominantly in complex electro-mechanical, software driven embedded systems, associated disposables and applications software in high reliability and human safety critical products from concept to development, distribution and post-market support. Prior to his current St. Jude Medical role, Mark was Vice President, Quality, Neuromodulation Division. Prior to St. Jude, Mark led Baxter Healthcare's Renal Business Design Quality Engineering and Global Service Quality organizations. Prior to Baxter, Mark served in Quality leadership roles at GE Healthcare, Alcon Laboratories, Adaptec, Abbott Laboratories and Texas Instruments. At the start of his career, Mark served in the U.S. Army as an Ordnance Corps ammunition and nuclear weapons officer.

Mark has a B.S. in Nuclear Engineering from Texas A&M University. Mark is active in the American Society for Quality (ASQ) where he is a Senior Member and holds certifications in quality management, quality engineering, software quality engineering and quality auditing. He was Chairman for five International Conferences on Software Quality (ICSQ), sponsored by the Software Division of ASQ. Mark also is a member of the IEEE. Mark has published and presented technical papers on quality and engineering topics a number of publications and conferences. Mark is a founding member and Past Chairman of the Dallas/Fort Worth Association for Software Engineering Excellence. Mark serves on the Texas A&M University Biomedical Engineering Advisory Board and on the Work Planning and Control External Advisory Board for Sandia National Laboratories. He and his wife live in the North Dallas area and enjoy traveling and scuba diving.

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Agenda

- FDA Inspections Overview
- Levels of Regulatory Action
- Warning Letter Impacts on Business
- Responding to 483s and Warning Letters
- Warning Letter Clearance Approach
- Warning Letter Re-inspection Preparation
- Warning Letter Re-Inspection
- Warning Letter Closure
- Concluding Remarks

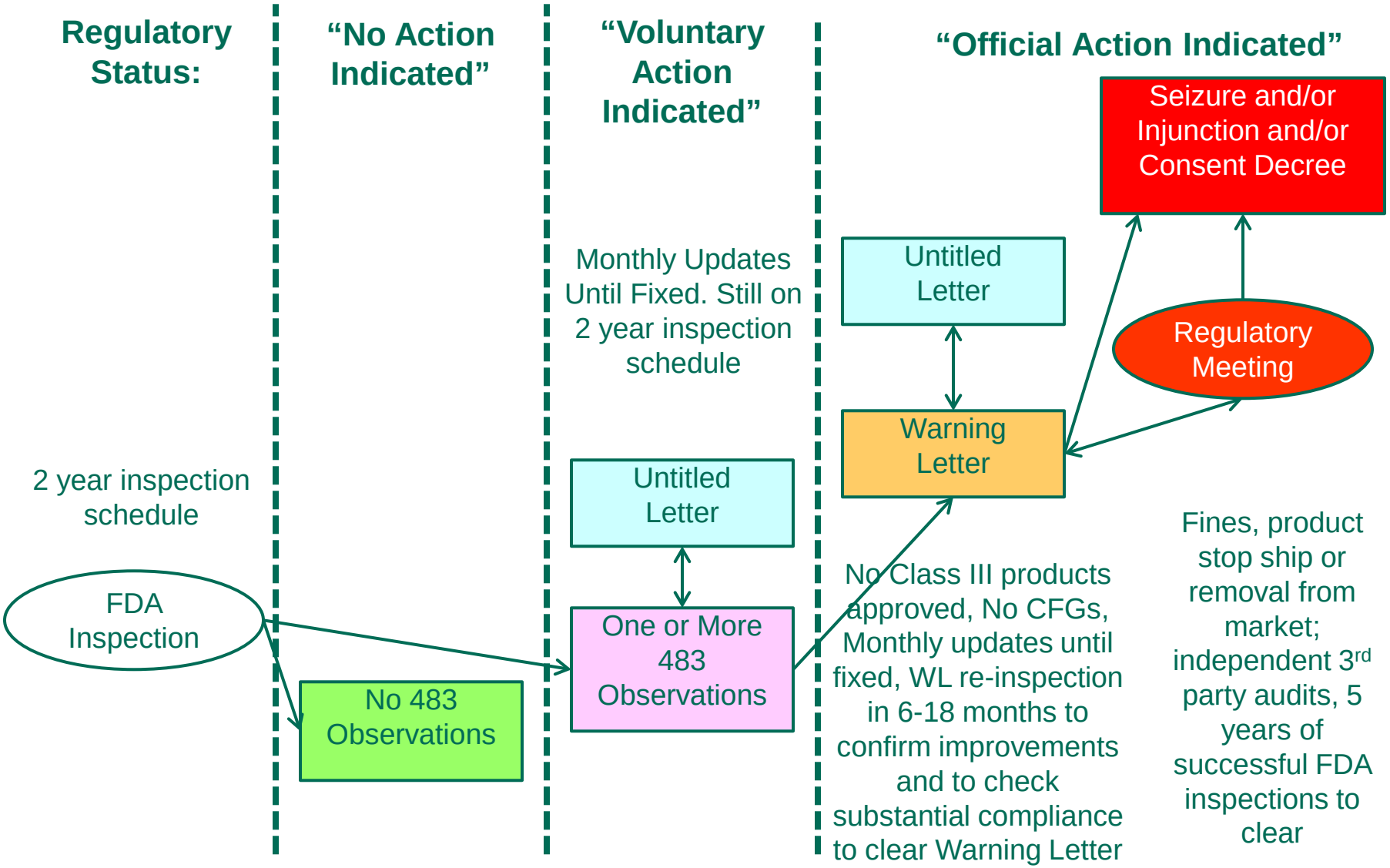
FDA Inspections Overview

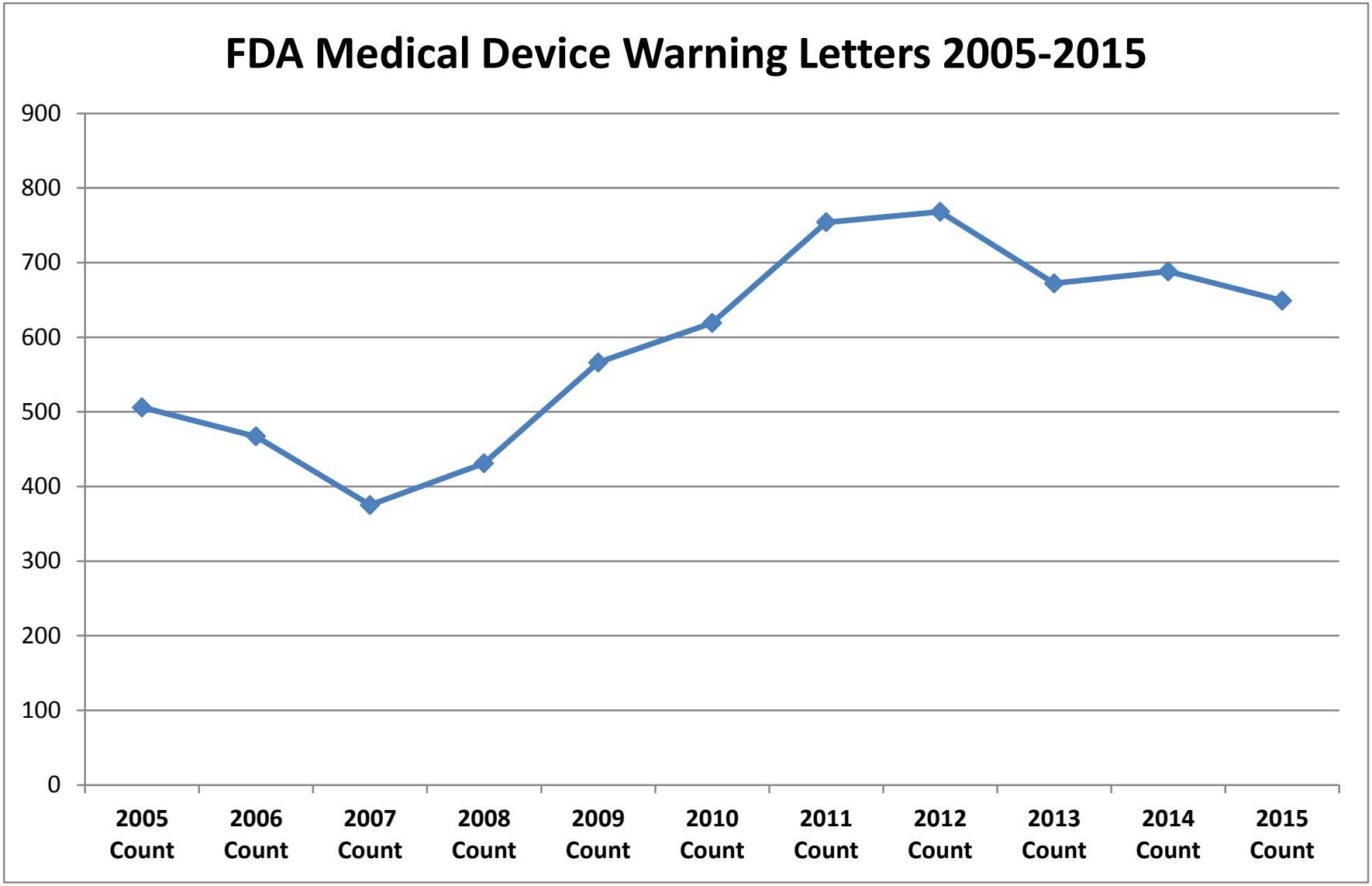
- Office of Regulatory Affairs (ORA) - lead office for FDA field activities
  - >4,400 ORA personnel in >200 locations, including Office of Criminal Investigations (OCI)
- Inspections are mandated by law, every 2 years for Class II and III device manufacturers based on:
  - Risk
    - Device risk – implantable, life supporting, life sustaining, new device, history of violations
    - MDR rates
    - Recalls
  - Compliance - follow up to a regulatory action
  - Complaints - device customers, patients, other industry
- Investigator may announce inspection 3-5 days in advance; a courtesy, not required
- Investigator presents credentials and FDA 482, Notice of Inspection
- Investigator conducts inspection with Quality Management Representative (QMR)

FDA Inspections Overview (cont)

- Investigator uses TurboEIR to create FDA 483, Inspectional Observations
- Investigator issues 483 to Management With Executive Responsibility (MWER)
- Investigator drafts Establishment Investigation Report (EIR)
- Firm sends 483 responses to FDA District Director
- District Director of Compliance and investigator discuss violations
- If warranted, District submits Warning Letter recommendation to CDRH Office of Compliance.(OC)
- If agreed, CDRH OC and District draft Warning letter
- FDA District Director sends Warning Letter to Firm – may go to CEO
- Firm sends Warning Letter Responses
- FDA may send Untitled Letter if Warning Letter Responses are not adequate or clear

Simplified Regulatory Action Escalation





Regulatory Compliance Experience

- ISO Registrar/Notified Body
  - Registration, Surveillance, Unannounced
- Country-Specific Competent Authorities
  - Brazil, Czech Republic, Korea, etc.
- FDA Inspections
  - Pre-Approval Inspections (Class III - 510(k), PMA, PMA Supplement)
  - Quality System Inspection Technique (QSIT) [Level 1 and Level 2]
  - Bioresearch Monitoring (BIMO) [Clinical Trials]
  - Directed/For Cause
- FDA Warning Letters
  - Alcon Labs, Refractive Surgery Div — Led Overall Resolution
  - GE Healthcare, Healthcare IT Div — Led Design and Service
  - Baxter Healthcare, Renal Div — Led Coding, Software and Mfg
  - St. Jude Medical, Neuro Div — Led Overall Resolution
  - St. Jude Medical, CRM Div — Led Overall Resolution

Alcon Labs, Refractive Surgery Div; Orlando, FL

- FDA District: Florida Inspection: Jan 2005 Warning Letter: Apr 2005
- Warning Letter Issues:
  - Complaint Investigation
  - Complaint Evaluation for MDR Reporting
  - MDR Reporting Within 30 Days
  - Failure Analysis of Field Service Parts
- Direct Impacts
  - No Class III PMAs or PMA Supplements Cleared
  - No Certificates for Foreign Governments Approved
- Warning Letter Cleared: August 2006
  - 19 months from Inspection, 16 months from Warning Letter

GE Healthcare, Healthcare IT Div; Barrington, IL

- FDA District: Chicago Inspection: May 2008 Warning Letter: Aug 2008
- Warning Letter Issues:
  - CAPA Data Sources
  - Design Changes
  - Software Manufacturing First Article Inspections
  - Complaint Investigation and Evaluating Servicing Activities for Complaints
  - Complaint Evaluation for MDR Reporting
  - MDR Reporting Within 30 Days
  - Corrections and Removals
- Direct Impacts
  - None stated - Class II, 510(k) Products
- Warning Letter Cleared: Dec 2009
  - 19 months from Inspection, 16 months from Warning Letter

Baxter Healthcare, Renal Div; McGaw Park, IL

- FDA District: Chicago Inspection: Dec 2009 Warning Letter: Jun 2010
- Warning Letter Issues:
  - Complaint Evaluation for MDR Reporting
  - MDR Reporting Within 30 Days
  - CAPA Investigation Timeliness, Completeness and Effectiveness of Corrective Actions
  - Complaint Coding
  - Complaints Derived from Device Logs and MDR Reporting
  - Manufacturing Materials
  - Deferred Software Defects
- Direct Impacts
  - No Class III PMAs or PMA Supplements Cleared
  - No Certificates for Foreign Governments Approved
- Warning Letter Cleared: Mar 2012
  - 27 months from Inspection, 21 months from Warning Letter

St. Jude Medical, Neuromodulation Div; Plano, TX

- FDA District: Dallas Inspection: Apr 2009 Warning Letter: Jun 2009
- Warning Letter Issues:
  - CAPA Investigation Timeliness, Completeness and Effectiveness of Corrective Actions
  - Design Verification, Design Validation and Design Output
  - Finished Device Acceptance Testing
  - Complaint Coding and Investigation
  - MDR Reporting and Supplements Within 30 Days
  - Manufacturing Quality Data Trend Analysis
  - Process Validation, Process Control and Test Method Validation
  - Corrections and Removals
- Direct Impacts
  - No Class III PMAs or PMA Supplements Cleared
  - No Certificates for Foreign Governments Approved
- Warning Letter Cleared: Aug 2014
  - 65 months from Inspection, 63 months from Warning Letter

St. Jude Medical, Cardiac Rhythm Mgmt Div; Sylmar, CA

- FDA District: Los Angeles Inspection: Oct 2012 Warning Letter: Jan 2013
- Warning Letter Issues:
  - Process Validation
  - Test Method Validation
  - Design Verification
  - Design History File
  - CAPA Effectiveness of Corrective Actions
  - MDR Reporting
- Direct Impacts
  - No Class III PMAs or PMA Supplements Cleared
  - No Certificates for Foreign Governments Approved
- Warning Letter Cleared: Sept 2014
  - 23 months from Inspection, 20 months from Warning Letter

Warning Letter Impacts on Business

- Class III Products
  - No Class III PMAs or PMA Supplements Cleared unless related to Warning Letter Response (recall corrective actions, complaint reductions, etc.
  - No Certificates for Foreign Governments Approved
- Remediation Costs
  - Direct consulting fees if supplemental expertise is needed
  - Temporary labor fees if additional resources are needed
  - R&D shutdowns if significant design control/DHF remediation needed
  - Manufacturing holds, market withdrawals or shutdowns if significant remediation needed
- Other Costs
  - Customer loss of confidence or competitor “marketing” of your Warning Letter
  - OUS Competent Authority scrutiny may impact imports or denial of approvals for new countries
  - Notified Body additional scrutiny

Responding to FDA 483s & Warning Letters

- READ THE OBSERVATION!!
- Define the correction of the specific finding and systemic corrective action in the commitments; include training when applicable
- Ideal response is to show completion of the commitment(s) with the response – no reason for FDA to escalate; e.g., modify procedures, release and conduct training and show copies in response
- If commitments cannot be completed with the response, make them:
  - Timely
  - Comprehensive – look at other affected products or systems and process
  - Reflect understanding of the observation specifically and in bigger context

Responding to FDA 483s & Warning Letters (cont)

- 483 Commitments
  - Correct for “Go Forward”
- Warning Letter Commitments (not all 483s may be on Warning Letter)
  - “OAI” Status means practices not substantially compliant
  - May Require 2-Year Retrospective Reviews/Remediation
- Complete cover letter, response and attachments in time to deliver to the FDA District Director no later than 15 business days from receipt
- A District Consumer Safety Officer will likely be assigned as primary point of contact for a Warning Letter for responses, monthly updates or other communication
- You may request a meeting with the FDA District, but unless there is something significant to discuss outside of the responses, do not expect agreement with a meeting

Warning Letter Clearance Approach

- Complete explicit 483 commitments
  - Specific fixes for observations
  - Systemic improvements to prevent recurrence – SOP updates, training, etc. – sometimes more
- Complete explicit Warning Letter commitments
  - Specific fixes for observations
  - Systemic improvements to prevent recurrence – SOP updates, training, evaluate applicability to other products and processes, etc. – holistic view with broad and deep corrective actions
  - “Retrospective Reviews” - correct select activities, documents and records for past two years – complaints, MDRs, recalls, design history files, etc.
- Monthly reports to FDA District to demonstrate progress on commitments and objective evidence for items completed.
- FDA may schedule interim inspections prior to completion of commitments, especially if products are Class III.

Warning Letter Re-inspection Preparation

- In addition to demonstrating completion of WL observations, we must be ready for full Quality System review during re-inspection to demonstrate “substantial compliance” to clear Warning Letter
- FDA District re-inspection will be broad and deep to ensure no other significant violations exist
- It is not uncommon for re-inspection readiness activities to be 10x or more the effort to resolve the specific commitments
- There is no need to disclose your re-inspection readiness activities in monthly reports
- FDA District will assume you are ready for re-inspection when you have completed all commitments and monthly reports stop
  - Therefore, plan to complete all preparations prior to the last monthly report
- Once you are ready for re-inspection, call assigned CSO and email your readiness for re-inspection

Quality Management System “Deep Dives”

- Conduct an in-depth review of each quality system element to identify any other issues which must be corrected prior to re-inspection
- Internal Approach - Independent Reviewers (practitioners from other company sites that are in substantial compliance) work with department personnel (Subject Matter Experts) to evaluate procedures, work instructions and historical records
- External Approach – Numerous consultants in this space
- SMEs are encouraged to identify any issues they are aware of
- 3-5+ review days per QMS element, depending on complexity and criticality
- Observations reviewed by Warning Letter Resolution Leadership Team to identify those requiring fixes
- Observations to be fixed will be tracked in weekly resolution team meetings along with FDA commitments

Key Issue Binders

- Proof Books
  - Each 483 and Warning Letter observation will have a “proof book” to demonstrate we completed each commitment
  - Contains observation, list of commitments and tabs for objective evidence of completing each commitment
  - Each Observation will have an assigned SME to present proof and answer questions during re-inspection
- Storyboards
  - Key CAPAs, controversial topics, anticipated FDA focus areas and other issues may have a storyboard binder
  - Especially useful for items where the formal records cannot be ordered in a way to give the best explanation
  - PowerPoint storyboard and associated reports, records, etc. to demonstrate work performed and due diligence
  - Each storyboard will have an assigned SME to present issue and answer questions during re-inspection

Front Room/Back Room Inspection Logistics

- Identify inspection personnel to man front room and back room roles - primary and backups; keep updated during preparation period
- Plan infrastructure – computers, printers, display screens, SME preparation areas, phones, switches and routers, FR/BR supplies, etc. – all pre-positioned and ready for FDA arrival
- Note: Use wired networking for back room activities, especially for documents sent to printer – wireless networks will come to a crawl or be unresponsive
- Conduct training of FR/BR personnel
- Conduct 2-3 FR/BR exercise sessions to gain proficiency
- Plan for as many as 3 investigators
  - Try to keep in main front room, but be prepared to break out into separate rooms if requested
- Define SME List for each Quality System area, CAPA, key issue, etc.

SME Role Play

- SME role play is probably the most critical activity to ensure inspection success
- Choose a SME that is knowledgeable of the area and issue, but knows how to discuss the work in a credible and effective way
- Role Play Before Inspection
  - Each proof book, storyboard and Quality System area SME (primary and backup) will have 3-5 role play sessions with different people to exercise story and answers to anticipated questions
  - SMEs will be coached on approach, presentation and handling questions
- Role Play During Inspection
  - For FDA requests not role played before inspection, there should be 2-3 knowledgeable people available in the back room who will role play individuals before going into the front room
  - Gives SME a chance to gather thoughts and obtain coaching on the best way to answer the question and present documents

Other Preparation Activities

- May use Corporate Internal Audit mechanisms or contract auditors to help gauge progress
- Conduct inspection training for site personnel – Dos and Don'ts
- Conduct 1 or 2 Mock Inspections
  - Use experienced front room personnel from other parts of the company or external consultants (former investigators)
  - Practice Front Room/Back Room in a more realistic exercise
  - Give SMEs an opportunity to present materials and answer questions from role play
- Intend to complete all commitments, deep dive observations and re-inspection preparations to request re-inspection from District CSO
- Note: Due to risk, other issues the FDA District is addressing, need to schedule FDA National Experts and normal work scheduling, it may take several weeks to six months for re-inspection to start

Warning Letter Re-Inspection

- Inspection is to verify completion of commitments, that corrective actions were sustained through systemic improvements and ensure there are no other significant violations
- In opening meeting presentation summarize the actions taken to complete each commitment (from monthly reports)
- Investigators may start with Warning Letter observations or may start in a normal Quality Systems Inspection Technique (QSIT) fashion
- At the conclusion of the inspection, ask the lead investigator if they will be recommending Warning Letter Closure; investigator may say “don’t know” or may defer to CSO

Warning Letter Closure

- After conducting inspection, the investigator's EIR draft will be reviewed by the FDA District and CDRH OC
- If the review determines all commitments were completed satisfactorily and the no other egregious violations were identified, then substantial compliance may be determined
  - Minor 483 items may not affect substantial compliance determination
  - Major 483 items or unresolved prior 483 or Warning Letter commitments may continue the Warning Letter (and OAI status) until the next inspection
- FDA updates the firm's status to VAI or NAI
- Many FDA Districts, but not all, follow FMD 145 to notify the firm that the Warning Letter is cleared
  - FMD 145 is the process for FDA to provide EIRs to the firm after inspection
  - During the OAI period the firm cannot receive the EIRs, therefore to receive the EIR(s) from the original and interim inspections signals Warning Letter Closure

Warning Letter Closure (cont)

- Some FDA Districts may send a specific Warning Letter closure letter, but it is not required
- A few weeks after the inspection, call the CSO and ask if the internal review is completed and if FDA intends to clear the Warning Letter
- If Warning Letter clearance is recommended by the District and agreed by CDRH OC, it may take 1-4 months from the re-inspection to receive the FMD 145, as the final inspection EIR must be completed and approved before release
- After Warning Letter Closure:
  - Celebrate!
  - Work to prevent backsliding to old ways
  - Share lessons learned with other company Divisions or sites
  - Beef up internal Audits
  - Review 483s and Warning Letters from competitors or similar businesses to keep up with FDA “raising the bar”

Concluding Remarks

- Business impact of Warning Letters can be substantial
- Conversely, if you are proactively compliant to the regulations, you may leapfrog competition while they are under an OAI status – use Quality and Regulatory Compliance as a competitive advantage
- Employee morale is likely low during remediation and re-inspection preparation; some will “bail” and some who cannot get on board with the new culture may need to be disciplined or terminated
- People who work through a Warning Letter together will “bond” and see it as a learning experience they won’t want to repeat
- FDA commitments and re-inspection preparation must be run like a program and with the highest priority
- Celebrate major milestones, as it may take many months or years for final closure
- Failing to successfully clear the Warning Letter at the first re-inspection may delay the next inspection more than a year
- After closure, work to prevent backsliding or stagnation that could result in another Warning Letter or Consent Decree

Questions?

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