“HOW TO DEAL IN A REGULATED ENVIRONMENT”

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AGENDA

- Origin of the FDA Medical Devices standard (21 CFR 820)
- Compliance strengthens Quality organization
- The “101” on FDA inspections
- Managing device registrations
ORIGINS OF THE FDA

- FDA’s Mission Statement
  - To serve and protect the American public health
  - “..promote and protect health by helping safe and effective products reach the market in a timely way .. monitoring products for continued safety after they are in use.”

- Pure Food and Drug Act passed in 1906
  - Passed to protect American’s from so called “drugs” that were being administered with no testing / verification for effectiveness

- Foreign Governments have modeled their agencies after the FDA
  - China / Brazil / Japan / Europe
FDA Overview

- Regulates over $1 trillion worth of products per year
- Regulates the safety and effectiveness of all drugs, biological products, animal drugs, cosmetic products, and medical devices
- Ensure medical and consumer products that emit radiation do no harm
- Large Scope, Small Team = Overwork
- Regulatory Procedures Manual
  - FDA internal procedures manual for personnel
MULTIPLE FDA CENTERS ALLOW FOCUS

- CDER – Center for Drug Evaluation & Research
- CDRH – Center for Devices and Radiological Health
  - Center that deals with Medical Devices
- CBER – Center for Biologics Evaluation and Research
- CVM – Center for Veterinary Medicine
- CFSAN – Center for Food Safety and Applied Nutrition
THE FDA INSPECTS:

- Vaccine and Drug Manufacturers
- Blood Blanks
- Food Processing Facilities
- Dairy Farms
- Animal Feed Processors
- Compounding Facilities
- Facilities that conduct Clinical Trials
- Laboratories that complete studies used for FDA approvals
- Foreign Manufacturing & Processing locations
**Types of FDA Inspections**

- **Pre-Approvals**
  - Completed once a company submits an application to the FDA to market a new product

- **Routine Inspections of regulated facilities**
  - The most common inspections
  - Frequent review of an organization's quality system and controls
  - May be announced or unannounced

- **“For Cause” inspections**
  - To investigate a specific problem that has come to the FDA’s attention
  - May be the result of poor response to a “Warning Letter” or “Medical Device Reportable” incident
  - Typically unannounced

“All inspections may lead to Form 483 observations”
Routine Inspections

- Periodically every 2-3 years
- May be announced or unannounced
- Typically cover all aspects of GMP (Good Manufacturing Practices)
- May be limited in scope
- FDA is Interested in Products and Processes
  - “Valid” Processes producing the “Correct” Products
  - Focus is not just the Medical Devices but also the intermediate products including “Data” & “Records”
  - No records = No evidence = No process
  - “We have no CAPA’s” good for you, not the FDA
COMPLIANCE LEADS TO STRONGER QUALITY ORGANIZATION

Key tenets:
- CAPA
- Complaints
- Records
- Document Control
- Mgt Representative

- Calibration
- Design History File / Records
- Process Control / Validation
- Data Analysis
- Risk Based Management
WHAT HAPPENS DURING A TYPICAL ISO AUDIT

- Audit date is pre-arranged between Client and Registrar
- Audit agenda set prior to arrival
- Client has influence on auditors
- Client has ability to influence audit “+” or “-”
  - Info shared
  - Steering auditor
  - Hold up findings to the “standard”
- Findings are not made public
- Ability to work with Registrar

WHAT HAPPENS DURING A TYPICAL FDA INSPECTION

- Audit date – little to no notice
- Inspection
  - CAPA Records
  - Complaint Records
  - Product Development Process / Device History Records
  - Supplier Management Records
- FDA inspectors are Federal Agents trained in inspection techniques
- FDA inspector writes up Form 483 Observations
- Response is critical
- Form 483 are public
- Warning letters are public
KEYS TO A SUCCESSFUL FDA INSPECTION

- Remember that the FDA investigator is a professional colleague...just doing their job
  - Don’t disagree or argue...rather, discuss issues
  - Be prepared to help the inspector and support the inspection
- Know where your key records / documents are and have readily available
  - Master Validation Plan
  - SOP listing
  - Organizational Chart
  - Facility Diagram
  - List of all CAPA’s for last 6mo-1yr
  - List of all Complaints for last 6mo-1yr
Typical Form 483s Observations

- CAPA Programs
  - Root cause / Corrective Action
  - Records associated with the CAPA
- Incomplete or inaccurate SOP’s
- Calibration
- Training Records
- Spreadsheets to control processes
- Lack of Process Controls
- Quality Unit deficiencies
- Inadequate batch failure investigations
- Lack of Follow up procedures
- Complaint Handling and resolution
- Inadequate records
How to respond to an FDA Inspection

- **Form 483s Observations**
  - Respond within 15 calendar days
  - No response is a Response!
  - Answer each observation clearly / concisely
  - No response or poor response may result in the following:
    - Warning Letter
    - Facility shutdown
    - Product withholding
  - Note – Form 483s are Public Record but not published
- If acceptable response is provided, will be reviewed at next inspection
- If unacceptable response is provided, may lead to a Warning letter
**SUMMARY FORM 483**

**Observation Response**

- Restate the Observation
- Assure the FDA with a compliance statement
- State commitment of the company to comply with the applicable laws and FDA regulations & to correcting compliance issues
- Thank the FDA for raising the Observation
- Define the corrective action (CA) plan - describe the action(s) that correct the specific observation and planned timing (note – do not need to include exhaustive detail)
- Define the preventive action (PA) to address any systemic concerns which may be part of the observation
- Note any risk or impact on product quality
- If applicable, state if the Observation resulted in the creation of a CAPA
HOT TOPICS FOR THE FDA

- **Increased Inspections of Foreign Manufacturing Locations**
  - China / India

- **Supplier Management**
  - Control over sub-contractors
  - Supplier selection
  - Supplier monitoring
  - Supplier records

- FDA is increasing number of foreign QS inspections (p. 6)
- China had the most foreign inspections (p. 7)
- 41% of domestic inspections resulted in recommendations for voluntary actions by manufacturers (p. 8-9)
- 10% included observations requiring compulsory actions (p. 8-9)
- 46% of foreign inspections resulted in recommendations for voluntary actions by manufacturers (p. 8-9)
- 15% included observations requiring compulsory actions (p. 8-9)
- Vast majority of observations involved problems with CAPA systems and insufficient production and process controls (p. 17).
THE TRUTH ABOUT LIVING IN A REGULATED ENVIRONMENT

- Expect to be “Inspected” and or “Audited” a great deal
  - Reichert has a minimum of 10 Audit / Inspections per year not counting ISO Audits
  - Routine Safety Inspections
  - Audits to support registrations of products in certain foreign markets
  - Customer audits

- How you view Audits / Inspections can affect the outcomes
  - “Have to” vs “Opportunity to improve”
  - “Hide” vs “Transparency”
KEYS TO SUCCESS IN A REGULATED ENVIRONMENT

- Top Management sets the tone for the company
- Quality & Regulatory Leadership help to set the vision / policy
- Know the laws for the industry and or country products are sold
- The Quality Policy is clearly communicated
- Have a Regulatory Policy that engages all levels of the organization
- Foster an open environment where inspections / audits are seen as areas for improvement
- Communicate / Communicate / Communicate
KEYS TO SUCCESS IN A REGULATED ENVIRONMENT

- Recognize that Quality / Regulatory are the best business practices
- Streamline processes
- Ensure records are properly documented and stored
- Avoid product recalls / lawsuits
- Use your systems!
  - Lack of CAPA’s is not an effective system
  - Lack of Audit findings is not an effective system
- Document / Document / Document
DEVICE REGISTRATION KEYS TO SUCCESS

- Ensure documentation to support FDA compliance are clear / concise and up to date
- Compliance to MDD requirements in Europe can provide a model for registration
- Work with a partner whose responsibility is knowing the regulations / laws for the country
  - Dealer / Distributors
  - 3rd Parties
  - Notified Bodies
SUMMARY

- Dealing in a regulated environment may be one of the most challenging environments
  - But, for those who can do it well, you can reap the rewards
- Be ready for the inspection / audit
  - Keep your system current & well documented
- See these as opportunities for improvement
  - Changing your mindset with change how you approach the audit / inspection
- Quality / Regulatory professionals are critical assets

ASQ – Certifications / Training for Quality Professionals
RAPS - Certifications / Training for Regulatory Professionals