What does Food and Drug Administration (FDA) Inspect?

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What is an FDA inspection?

- The Food and Drug Administration (FDA) conducts inspections and assessments of regulated facilities to determine a firm's compliance with applicable laws and regulations, such as the Food, Drug, and Cosmetic Act.
- The FDA is responsible for protecting public health by regulating human drugs and biological products, animal drugs, medical devices, tobacco products, food (including animal food), cosmetics, and electronic products that emit radiation.

What FDA Do?

Mission: Promote and Protect Public Health

- FDA's primary responsibility is to protect the American people from unsafe or mislabeled food, drugs, and other medical products and to make sure consumers have access to accurate, science-based information about the products they need and rely on every day.
- FDA/CDER (Center for Drug Evaluation and Research) ensures that safe, effective and high quality drugs are available for U.S. consumers.

Division of Drug Information (DDI)

- **Division of Drug Information** is CDER's focal point for public inquiries regarding human drug products.
- The mission of DDI is to optimize CDER's educational and communication efforts to our global community.
- We support the FDA's mission to promote and protect public health.

FDA Databases

- Drugs@FDA
- National Drug Code (NDC) Directory
- Orange Book
- Purple Book
- Drug Safety Labeling Changes (SLC) Database
- Drug Shortages
- Approved Risk Evaluation and Mitigation Strategies (REMS)
- Drug Safety Communications
- MedWatch

Who conducts inspections for FDA?

- The Office of Regulatory Affairs (ORA) is the lead office for all field activities at the FDA.

Who conducts inspections for FDA?

- Part of the Office of Regulatory Affairs
- To maximize compliance of regulated products and to minimize public health risk.
- Office of Criminal Investigations (OCI)

Who conducts inspections for FDA?

1. FDA investigators in FDA District Offices around the U.S.

2. FDA-trained Auditors from Conformity Assessment Bodies in the European Union (EU).

3. FDA-trained auditors from independent third parties accredited by FDA.

How does FDA decide who to inspect?

- Registration database identifies who manufacturers devices for distribution in the U.S.
- Listing database identifies what devices they distribute.
- FDA prioritizes inspections by risk and gives higher risk devices/situations a higher priority.

How does FDA decide who to inspect?

- Mandated by law, every 2 years for class II and class III device manufacturers.

  - Risk.

  - Follow up inspections to a regulatory action.

  - Complaints (public & industry).

What is high priority for inspection?

- Device manufacturers that:
  - Make Class III or Class II devices.
  - Make implantable devices and life supporting and life sustaining devices.
  - Recently introduced a new device to the market.
  - Have had significant violations in the past.

Does FDA notify the manufacturer of an upcoming inspection?

- FDA calls domestic manufacturers up to 5 calendar days before the inspection.
- FDA contacts foreign manufacturers 2 - 3 months in advance to schedule inspection.
- Manufacturer may be requested to send Quality System Manual or equivalent for pre-inspection review.

What happens when the FDA investigator arrives at the site?

- The FDA investigator will:
  - Ask to see the top management
  - Present credentials (identification as an authorized FDA investigator)
  - Issue FDA-482 "Notice of Inspection" (explains FDA's legal authority to inspect)

What happens during the inspection?

- Investigator may tour the facility to get an idea of layout, workflow, and areas that may need closer inspection.
- This helps the investigator decide how to organize the inspection

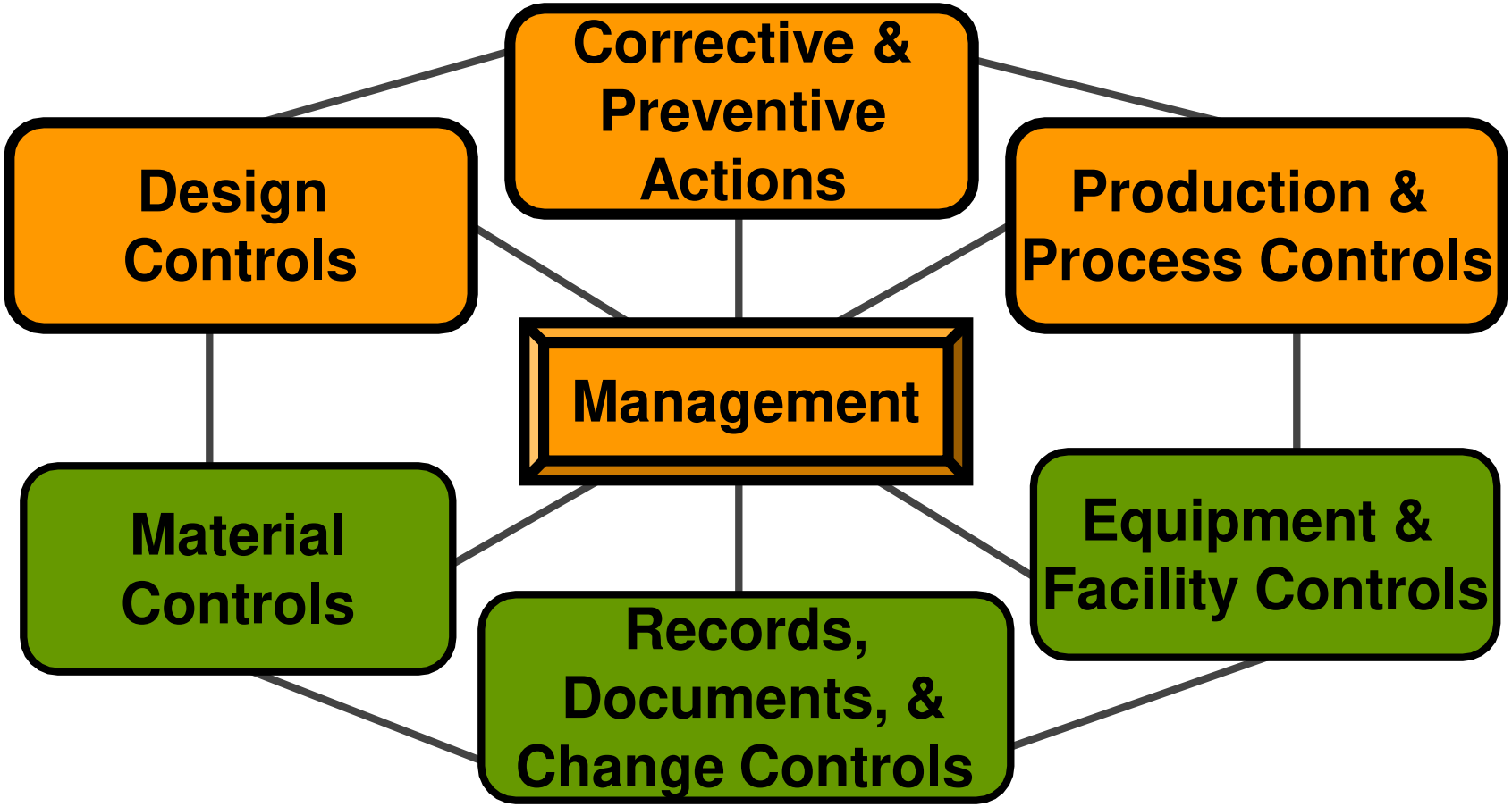
What happens next?

- The investigator will:
  - Gather information about size and structure of company, who are the responsible officials, what products are manufactured there
  - Evaluate the manufacturer's quality system using the Quality System Inspection Technique (QSIT)

What is Quality System Inspection Technique (QSIT)?

- Identifies 4 major subsystems to evaluate and states the purpose and importance of each subsystem
- Provides flowcharts and inspectional objectives to cover during inspection
- Offers advice on inspection
- Provides tables for statistical sampling of records for review

What are the four main subsystems?



Does FDA conduct different types of inspections?

- Investigator may conduct 1 of 3 types of GMP inspections for medical devices:
  - Level 1 – Abbreviated QSIT
  - Level2 – Baseline QSIT (Comprehensive)
  - Compliance follow-up
- "For Cause"

What is a Level 2 baseline (comprehensive) inspection?

- An inspection that:
  - Covers all 4 main subsystems
  - Is conducted when the firm has never had Level 2 inspection and every 6 years thereafter, resources permitting
  - Provides an overall evaluation of the firm's quality system

What is a Level 1 abbreviated inspection?

- An inspection that:
  - Is conducted after firm has had a Level 2 inspection, and quality system was in compliance with requirements
  - Covers CAPA plus one other major subsystem
  - Covers a different subsystem each time

What is a compliance follow-up inspection?

- An inspection that:
  - Is conducted to verify adequate correction of previous violations or document continuing violations to support possible regulatory action
  - Is conducted to follow up on information indicating serious problems at firm
  - May include elements of QSIT

What is a “for cause” inspection?

- Initiated at the request of CDRH, ORA Headquarters, Regional or District Directive

- Dictated by the source of information and may differ from typical QSIT approach

- These inspections are generally more in depth in particular areas than typical QSIT inspections
- Conducted as the need arises
  - Important note in CP, if the Investigator encounters a serious public health risk during the QSIT inspection the investigator may switch to a for cause inspection

What does FDA look for in the Management Subsystem?

- Has a Quality Policy been established?
- Has a management representative been appointed?
- Has Management with Executive Responsibility conducted management reviews?

What does FDA look for in the Management Subsystem?

- Have quality audit procedures been established and have quality audits been conducted?
- Has a quality plan been established?
- Have quality system been procedures established?

What does FDA look for in the Design Control Subsystem?

- Have design procedures and plan been established?
- Have design inputs or requirements for device been identified?
- Have design outputs or specifications for device been developed?
- Has design verification been conducted?
- Has design validation been conducted?

What does FDA look for in the Design Control Subsystem?

- Has software been validated?
- Has risk analysis been carried out?
- Have design reviews been conducted?
- Has design transfer to manufacturing been completed successfully?

What does FDA look for in the Corrective and Preventive Action Subsystem?

- Have CAPA procedures been established?
- Are sources of data analyzed to identify nonconforming product and quality problems?
- Is a statistical analysis conducted across data sources?
- Are investigations conducted to identify root cause of failures?

What does FDA look for in the Corrective and Preventive Action Subsystem?

- Is nonconforming product controlled?
- Are corrective actions and preventive actions appropriate and effective and carried out?
- Are those responsible are told about CAPA activities?
- Does management review CAPA activities?

What does FDA look for in the Production and Process Control Subsystem?

- Are processes controlled and monitored?
- Are rejects and nonconforming product handled appropriately?
- Is equipment adjusted, calibrated and maintained?

What does FDA look for in the Production and Process Control Subsystem?

- Are all manufacturing processes validated or fully verified?
- Is software validated?
- Are production employees trained and qualified?

What about the other subsystems?

- The other three subsystems are covered through links with the four main subsystems:
  - Records, documents and change control
  - Facility and equipment control
  - Material control

What happens at the end of the inspection?

- The investigator will:
  - Meet with management to discuss the inspection
  - Present the FDA 483 "List of Observations" of any significant observations
  - Discuss the observations

What happens at the end of the inspection?

- Turbo EIR?
  - Links citations to underlying regulations and statutes
  - Provides uniform FDA-483s and EIRs
  - Improves data analysis

What happens at the end of the inspection?

As of 1997, the FDA established an annotation policy for medical device inspections. The investigator(s) should offer to annotate the 483 with one or more of the following:

- *Reported corrected, not verified*
- *Corrected and verified*
- *Promised to correct*
- *Under consideration*

What should the manufacturer do after the inspection?

- Send a letter to FDA identifying how they have corrected observations or will correct them
- Provide documentation of any corrections that have been completed
- Provide a timetable or estimated completion date for future corrections

What happens next?

- Investigator returns to office to write an "Establishment Inspection Report" or EIR
- Inspection is classified based on inspectional findings
- Compliance officer decides whether to recommend regulatory action

How does FDA classify inspection reports?

- NAI – No action indicated
- VAI – Voluntary action indicated – some deficiencies identified but not serious
- OAI – Official action indicated – serious deficiencies identified, and FDA must take action to assure correction

What actions can FDA take to address OAI inspections?

- Warning Letter
- Seizure
- Injunction
- Civil penalties
- Criminal penalties

Warning Letter

- FDA sends "Warning Letter" describing manufacturer's violations of FDA regulations and requesting a reply within 15 days

Warning Letter

- FDA inspects the manufacturer 6 - 12 months after sending the Warning Letter to confirm correction of deficiencies

Summary

- Who conducts inspections for FDA
- Quality System Inspection Technique (QSIT)
- How FDA conducts inspections
- What should a manufacturer do after an inspection
- Enforcement actions FDA can take when manufacturers do not comply with regulation

FDA Inspections
in Clinical Research Companies

Objectives

- Enhanced knowledge regarding the preparation and process and close out of an FDA inspection.
- To ensure that all studies conducted within TJU are compliant with GCP and FDA guidelines.
- Comprehensive understanding of the documentation review process that is a focus for the FDA during an inspection.
- Proper preparation and organization of a clinical research trial prior to commencement of the study.

Definitions

- **Audit** means a "***systematic and independent examination of trial-related activities*** and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)" (ICH E6 Section 1.6).
- **Inspection** means an "***act by a regulatory authority(ies) of conducting an official review of documents, facilities, records, and any other resources*** that are deemed by the authority(ies) to be related to the clinical trial and that may be located at the site of the trial, at the sponsor's and/or contract research organization's (CRO) facilities, or at other establishments deemed appropriate by the regulatory authority(ies)" (ICH E6 Section 1.29).
- **Monitoring** means "***the act of overseeing the progress of a clinical trial, and of ensuring it is conducted, recorded, and reported in accordance with the protocol***, standard operating procedures (SOPs), GCP, and the applicable regulatory requirement(s)" (ICH E6 Section 1.38).

Investigational New Drug (IND)

- An Investigator IND is submitted by a physician who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed.
- A physician might submit a research IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.
- Form FDA 1571

Investigational Device Exemption (IDE)

- An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. Clinical studies are most often conducted to support a pre-market approval (PMA).
- Investigational use also includes clinical evaluation of certain modifications or new intended uses of legally marketed devices. All clinical evaluations of investigational devices, unless exempt, must have an approved IDE before the study is initiated.

Site Selection

- The FDA typically inspects the top enrolling site and randomly picks 10% of the remaining sites for inspection.
- The frequent occurrence of “outlier” data
- High/low numbers of participants responding to the study treatment
- High numbers of dropouts
- High numbers of adverse event (AEs/SAEs)
- High numbers of Protocol Deviations
- The volume of work performed by the clinical investigator

Additional Triggers

- High enrollment (especially in a short time)
- Few adverse events/or high adverse events
- Results different from other sites
- Patient complaints
- Investigators with many studies
- Investigator on study outside of specialty
- Sponsor reports poor quality data or other difficulties
- Most inspections are triggered by New Drug Application (NDA) and can occur after 1 year when drug has already been approved.

Notification of an Inspection

- Generally, the FDA investigator will notify the principal investigator by phone and establish a date for the inspection.
- The FDA inspector will usually request that the inspection take place within **10 days.**
- Remember to document all phone calls and correspondences with the FDA.

Notification with Company

- Vice President for Research
- Director
- University Senior Counsel and Corporate Compliance Officer
- Hospital Administration, *if applicable*
- Department Chair
- Executive Director of the Clinical Research Organization
- Manager of Clinical Trials Quality Assurance in the Clinical Trials Office
- Sponsor (Drug or Device Trial)
- All Key Personnel on the study

Role of Regulatory Coordinator

- Provide all IRB submissions [original, amendments, annual reviews, final report (if applicable), FDA Form 1572, IRB approval letters, all protocol versions, all consent versions, all IB versions, Financial Disclosure Forms, Delegation of Authority Log, Documentation of Training, CVs and MLs, etc.] and ensure that everything is clearly organized in the SMF ("Regulatory Binders").
- Inform IRB, study personnel, ORA, IDS Pharmacy, sponsor (if applicable), and any other necessary TJU personnel of upcoming visit.
- Have available applicable SOPs organized, and ensure they are finalized and updated, available if requested.
- ***Have a list of all of the PI's studies***, including protocol number, protocol title and IND/IDE number, name of sponsor, and study dates.
- Obtain the investigator agreements

Role of the Study Coordinator

- Carefully review all study documents, including source documents, CRFs, AE/SAE documentation, UAP documentation, consent forms and documentation of consent process, eligibility documentation, etc.
- Ensure that everything is documented and NTFs are provided for anything requiring additional explanation.
- Request subjects' medical records to verify diagnoses, eligibility criteria and any interfering medication.
- Are case histories attributable, legible, contemporaneous, original and accurate, complete, consistent, enduring and available (ALCOACCEA)?
- Did the PI follow the protocol- inclusion/ exclusion criteria, randomization, required procedures & evaluations, administration of investigational product (time frame and dosage), frequency of observations??
- List of all participants screened, enrolled, name, study ID, date enrolled and completed.

Pre-Visit Preparation

- Quality Assurance Team will assist with the preparation of the inspection; FDA Inspection Checklist
- Regulatory Specialist Team
- All correspondence from the IRB, Study Team, Sponsor, Compliance, Regulatory Team
- Make sure all documentation is available (policies (SOPs), source documents, CRFs, sponsor, regulatory, IRB)
- Resolve any outstanding issues, data correction, NTFs and Memo to File
- Notify sponsor, IRB, University Council, Investigational Drug Service (IDS)

Study Housekeeping

- All binders with identifiable information need to be stored in a locked and secure area.
- Study drug / device needs to be stored in a locked secure area away from regular inventory and only those on the study team may have access to this area.
- All enrollment spreadsheets must be password protected with only study team members having access to this spreadsheet, especially if kept in a shared drive.
- Do not forward enrollment logs in emails with any PHI.
- Ensure that all SOPs and DSMP are up to date and available as a reference during the inspection.
- No white out – cross through with one line – date and initial.

Essential Documents

- Informed Consent –Informed consent process should be documented in the physician progress record and/or a memo to file with the consent *(GCP section 1.28)*
- DOAL, Training Log, Updated CVs, 1572, all versions of protocols, ICFs, IBs.
- IND Safety Reports
- Inclusion/Exclusion Criteria
- Toxicity / AEs-SAEs / Dose Escalation or reduction
- Disease Outcome / Progression or regression of disease
- Data Timeliness

Form 1572

- The Statement of Investigator, Form FDA 1572 (1572), is an agreement signed by the investigator to provide certain information to the sponsor and assure that he/she will comply with FDA regulations related to the conduct of a clinical investigation of an investigational drug or biologic. The most recent version of the 1572 is available online at http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM074728.pdf.

Form 1572 continued…

- The 1572 has two purposes:
- 1) to provide the sponsor with information about the investigator's qualifications and the clinical site that will enable the sponsor to establish and document that the investigator is qualified and the site is an appropriate location at which to conduct the clinical investigation, and
- 2) to inform the investigator of his/her obligations and obtain the investigator's commitment to follow pertinent FDA regulations.
- Whenever a sponsor selects a new investigator to participate in a clinical investigation that is being conducted under an IND, the sponsor must obtain a completed and signed 1572 before permitting the investigator to begin participation in the clinical investigation (21 CFR 312.53(c)).

First Meeting with the Inspector

- Arrive ahead of time at designated area and wait for inspector.
- Arrange for an empty conference room that is quiet and away from casual conversations.
- FDA inspector may ask to be given a tour of the facility; the designated escort should stay with the inspector at all times.
- Study Team preparation – Availability of all Key Personnel on the study for meetings and know specific roles on the study.
- Upon arrival to the site, the FDA investigator will display FDA his/her FDA credentials and issue a completed form FDA 482 (Notice of Inspection).
- Initial meeting is typically 30-60 minutes depending on enrollment and complexity of the study.

Initial meeting…

- Be positive, confident and honest
- Listen carefully to the question, and wait until the inspector has finished the question. Allow silence if needed.
- Only offer information that is specifically asked
- Do not sign affidavits
- Relax

During the Audit

- The PI should make him/herself available each day of the inspection; typically there is a morning and afternoon meeting at the conclusion of the day.
- Verification of compliance with the regulations governing the use of investigational products and human subject protections (21CRF parts 50, 56, 312, and/or 812) by inspecting records and speaking with key personnel involved in the conduct of the study.

The FDA will always look for…

- ***Principal Investigator Oversight!!!***
- It should be transparent to the inspector that there is principal Investigator oversight within the clinical trial.
- Study Coordinators should schedule regular meetings with your PI and have him/her sign source documentation when necessary.
- PI Signature for inclusion/exclusion eligibility criteria.

What does the FDA review?

- Consents – accurate dates, consent versions at time of consent, only those delegated to consent on the DOAL; DOALs, Training forms;
- Source Documentation, Case Report Forms
- Timely SAE/AE reporting; resolution of SAE/AE
- Verify diagnosis, eligibility, progress notes of physician, hospital chart, nursing chart.
- Determine if any potentially interfering medication prohibited by protocol was taken.
- Protocol Deviations
- Determine proper follow up as outlined in protocol.
- Any internal monitoring or audits with corrective and preventative action plans (CAPA)
- Pharmacy/ Medical Device Logs (Study article)
- All Correspondence with the IRB, Study Team, sponsor, etc…

Documentation for consenting

- PI or Sub I: Documentation of consenting process should be written in the attending progress record.
- Study Coordinator: Consenting checklist that all aspects of the consenting process took place; ensure that the date and checklist and ICF match.
- Inclusion/Exclusion – Eligibility checklist with PI signature

Adverse Event Grading -

- If the adverse event is not serious, it must be added to the AE log and submitted at time of Continuing Review.
- If the AE is related or possibly related to the study treatment or procedure, the event must be reported to the IRB within 48 hours (24 hours if it is a grade 5), from the time of notification or knowledge using the eSAE system.
- Adverse Event Grade refers to severity as per the Common Terminology Criteria for Adverse Events (CTCAE) created by the *US Department of Health and Human Services, National Institutes of Health, National Cancer Institute*.

Grade 1 = Mild / Grade 2 = Moderate / Grade 3 = Severe

Grade 4 = Life-threatening or disabling / Grade 5 = Death

Serious Adverse Event (SAE) is judged to be grade 3, 4 or 5. and is defined (21 CFR 314.80) as any serious adverse drug experience that results in any of the following:

- Death
- Life threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability /incapacity
- Congenital anomaly/birth defect
- When based upon medical judgment, they may jeopardize the patient or subject requiring medical or surgical intervention to prevent on the outcomes listed in this definition. (ie. Bronchospasm)

Test Article Accountability

- Account for every pill, IV medication or device
- Receipt, dispensing, administration, return, destruction
- Patient diaries
- Administered per protocol
- Stored under the correct conditions, ambient or refrigeration
- IND/IDE – Lot batch #s / Authorization to ship/use unapproved drug/device / Expiration Dates / Locked away from SOC medication or device area.
- Administration → Safety and Efficacy

Laboratory

- Clinical Laboratory Improvement Amendments (CLIA)
- Normal Reference Ranges
- Equipment, Refrigeration (Correct temp), Processes
- Calibration/Temp of centrifuge
- Logs for processing and shipment

Inspection Process

- Reserve a room with lots of desk space away from other casual conversation
- Set up system of keeping confidential data secure
- Give brief, focused answers
- Point person will document all interviews, requests, communications, questions and answers
- Make a two copies of any document requested
- Begin an Inspection File
- Inspector will almost always begin with the review of consent forms, eligibility criteria, training logs, and DOAL
- Study coordinator should keep PI informed of what is happening during the inspection.

Inspection Process

- Provide only documents specifically requested by the inspector for review. Document all requests, make two copies of all documentation requested.
- All copies provided should be stamped "Confidential"
- If the FDA insists on taking photographs, take duplicates at the same time.
- Length of inspection is dependent on how many patients are enrolled or if there is a specific concern with the study.
- Typically an inspection can last from 3-7 days for routine visit; 7+ days for directed visit.

Exit Interview

- The FDA will usually hold an exit interview at the conclusion of the inspection. If serious deficiencies have been found during the inspection and Inspection Observations form 483 will follow from the regional office, listing the deficiencies.
- During this meeting, the PI will seek to correct any errors in the findings. Both the FDA and the PI will make sure everything is clear and understood.
- Observations, comments, and commitments will be noted in the escort inspection notes.

Most Common Deficiencies

The most commonly identified deficiencies include:

- Failure to follow the investigational plan
- Protocol deviations (and failure to properly document and report deviations)
- Failure to ensure that informed consent was obtained in accordance with 21 CFR 50
- Failure to maintain accurate, complete, and current records
- Lack of appropriate accountability for investigational agent
- Failure to obtain IRB approval
- Inclusion / Exclusion Criteria

Observations and Reports

- Classification of EIRs
  - OAI – Official Action Indicated
  - VAI – Voluntary Action Indicated
  - NAI – No Action Indicated
- Form FDA 483, Inspectional Observations (End of Inspection)
- Establishment Inspection Report (EIR) – Final Report
- Site responds with corrective actions and preventative actions (CAPA) within 15 days
- Close out letter

What is a 483?

- An **FDA – 483** is a Statement of deviations from federal regulations that requires a verbal response as well as a written response.
- Remember that it is CRITICAL to respond to an FDA 483 within 15 days. If you fail to respond to cGMP regulations violations in that time, your response to FDA will not even be opened.
- Findings should be discussed with the inspector and try and resolve the negative observations before they leave the site.
- A good response with the 483 may prevent a Warning Letter.

483 continued…

The formal response to the 483 must include:

- Management commitment to address the deficiencies in a timely fashion
- Specific details about each deficiency and how the company plans on addressing the issue including the underlying root cause
- Systemic issues
- Timeframe for completion
- Objective evidence to support the corrections

Responding to a 483

When you send in your 483 response, you should send it to the district office and to the CDRH or CDER. And make sure your response letter includes these elements:

- A reasonable deadline for corrective actions
- Take a ‘global response’ action if the observation can affect other areas and systems
- Include all response details and attachments
- Be complete and comprehensive
- Address any disagreements with observations
- Copy the investigator on the entire response package as a courtesy

Warning Letters

Both 483s and Warning Letters are public notifications and cab be viewed on the FDA website.

- The FDA issues a warning letter when it believes a investigational site has significantly violated FDA regulations. A Warning Letter indicates that higher FDA officials have reviewed the observations and that a serious violation may exist. The warning letter describes the violation, issues a demand for corrective action, and includes a deadline for responding with a corrective action plan.
- The investigational site must formally acknowledge receipt of the warning letter and has 15 days to respond to the FDA. Typically, along with the formal response, the investigational site includes a Corrective and Preventative Action Plan describing the specific actions to be taken and milestones for completion.

FDA warning letter for Investigator-initiated trial *(example)*

- Failure to ensure that informed consent is obtained in accordance with **21 CFR 50** and failure to properly document informed consent.
- Failure to conduct the investigation in accordance with the investigational plan.
- Failure to prepare and submit complete, accurate, and timely reports of unanticipated adverse device events.
- Failure to maintain accurate, complete and current records of receipt, use, or disposition of a device.

General Information about a Warning Letter

- Warning Letters are *not* final agency action
- –"…failure to correct *may* result in subsequent action such as seizure, injunction, civil money penalties, prosecution"
- –They are informal and advisory in nature
- Commitments to correct an observation at the conclusion of an inspection (FDA-483) may not preclude a Warning Letter
- It is management's responsibility to ensure all requirements of the Act are being adhered to – not just those identified in the Warning Letter
- Typically addressed to top management to ensure they know the seriousness by which FDA considers these observed violations
- It is management's responsibility to ensure adequate resources are available to fully correct the violations and prevent their recurrence
- A Warning Letter is the agency's principle means of achieving prompt voluntary compliance with the Federal Food, Drug and Cosmetic Act (the Act).
- FDA Regulatory Procedures Manual/ Chapter 4: Advisory Actions

Corrective and Preventative Action Plan (CAPA)

- A CAPA is written to identify a discrepancy or problem in the conduct of the clinical research study, note the root cause of the identified problem, identify the corrective action taken to prevent recurrence of the problem, and document that the corrective action has resolved the problem.
- In general, the tone of CAPA should be forward-looking and not seek to explain an error discovered in the conduct of a clinical research study.
- For example, it may be appropriate to: Clarify or add information regarding site specific regulatory file requirements, Clarify or add information regarding source document standards, Document and address any issue that is protocol- and/or site-specific that cannot be resolved without a change from previous procedures.

CAPA

Key things need to be included in a CAPA:

- 1) Root Cause Analysis: A class of problem solving methods used to identify the root causes of problems or events.
- 2) Corrective Action: Immediate action to a problem that has already occurred or has been identified.
- 3) Preventative Action: Taken to eliminate the root cause of a potential problem including the detection/identification of problems.
- ***Be Transparent***

Possible Consequences

- Study put on hold
- Re-inspection
- Rejection of study data
- Warning letter (Not following regulations)
- Restriction/Disqualification of investigator
- Increased risk to subjects
- Fine for the institution

Key Take Away

- The FDA could focus on any aspect of a clinical study; however, a consistent focus in documentation will be Informed Consent, DOALs, Training log, 1572, Timeliness of SAE/AE reporting, thorough knowledge of protocol, internal monitoring with any necessary corrective action and preventative plans.
- Observation for Principal Investigator Oversight!!
- Consistency in data from specific source documentation.
- Signatures, dates and times.

Compassionate Use

When a patient does not meet the inclusion criteria for a clinical trial, most compassionate drug use is for patients who meet all of these conditions:

- Have advanced disease
- Have used standard treatments and they have not worked
- Are not eligible for any clinical trial that's in progress
- Have no other treatment options
- Have a type of cancer for which there's reason to expect the investigational drug will help
- Are likely to have benefits that outweigh the risks involved

Compassionate Use

Before a patient or group of patients can get an unapproved new cancer drug outside of a clinical trial, 2 things MUST happen:

- The owner (sometimes referred to as the sponsor – most often a drug company) of the new, unapproved drug must agree to allow the use of their drug outside of a clinical trial.
- The FDA oncology medical officer in charge of overseeing the new drug's development must approve the use of the drug for that person or group.

*** PI and a physician not involved in the direct care of the patient must send in letters with medical history for sponsor and FDA review.*

Emergency Use - Drug

- Emergency use is defined as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval [21 CFR 56.102(d)]. The emergency use provision in the FDA regulations [21 CFR 56.104(c)] is an exemption from prior review and approval by the IRB.
- The exemption, which may not be used unless all of the conditions described in 21 CFR 56.102(d) exist, allows for one emergency use of a test article without prospective IRB review. FDA regulations require that any subsequent use of the investigational product at the institution have prospective IRB review and approval.

Emergency Use - Device

Requirements for Emergency Use

Each of the following conditions must exist to justify emergency use:

1. the patient is in a life-threatening condition that needs immediate treatment;
2. no generally acceptable alternative for treating the patient is available; and
3. because of the immediate need to use the device, there is no time to use existing procedures to get FDA approval for the use.

***Must notify the IRB and the sponsor via phone and as soon as possible with follow up letters within 5 working days to the IRB and the sponsor.*

FDA Inspections and Avoiding Common Mistakes in Clinical Research

Objectives

- Describe how FDA inspects clinical trials
- Discuss the most common mistakes FDA finds during inspections
- Suggest actions to prevent study problems

FDA's Bioresearch Monitoring Program (BIMO) Inspects....

Clinical Investigators

Sponsors/Monitors/Contract Research Organizations

Institutional Review Boards

Nonclinical Laboratories

When are BIMO Inspections Conducted ?

- Submission of marketing applications NDA/BLA/PMA/other
- Referrals from Center staff
- Referrals from other parts of FDA
- Complaints from sponsors, IRBs, and consumers
- Surveillance of ongoing studies under IND / IDE

FDA Inspection Assignment Package

- Background information
- Protocol
- Signed Form FDA 1572 (drug/biologic) or investigator agreement (medical device)
- Listings of individual subjects' data
- Adverse events
- Informed Consent Form
- Number of subjects enrolled
- Site specific information (deviations, outcomes, etc.)

Inspection Logistics

The FDA investigator will call to announce the inspection and request that ALL documents should be available for the inspection.

You arrange for a place for the FDA investigator to work and access to a copier.

The FDA investigator is required to show credentials to the most responsible person, and present a Form FDA-482 “Notice of Inspection” for domestic inspections. There is an opening interview.

The FDA investigator will review documents. Please make time each day to meet with the FDA investigator to answer questions.

FDA Review of Records

- Protocol and amendments
- Informed consent forms
- Drug accountability records
- Correspondence with Sponsor and IRB

  IRB Approvals & Progress reports & Adverse Event reports
- Case Report Forms
  - How data are recorded and corrected
  - Compare to source documents
- Supporting Files (Source Documentation)
  - Hospital/clinic chart, labs, diaries, etc.

Exit Interview

- Discuss inspection findings
- May issue a Form FDA-483 “Inspectional Observations”
  - Represents investigator’s observations of deviations from federal regulations for clinical investigators; is not a final FDA decision.
- Your verbal responses to Form FDA 483
- Your letter responding to the issues should be received within 15 days to be considered in deciding FDA’s actions.

After the Inspection...

- The inspection report is written by the FDA investigator and sent to the Center.

- The Center evaluates the report and determines the corrective action, and classifies the inspection:

  NAI = No Action Indicated, or

  VAI = Voluntary Action Indicated, or

  OAI = Official Action Indicated

- We write a letter to the inspected party following most inspections
- OAI inspections have consequences (warning letter, etc.)

Most Significant Violations

- Enrollment of ineligible subjects
- Violation of protocol affecting subject safety
- Extensive data corrections and questionable changes
- Inadequate oversight of study personnel
  - *Inappropriate delegation of authority*
  - *Poor oversight of satellite sites*
- No informed consent
- Failure to communicate with IRB
- Falsification

Sponsors are Required to Monitor the Studies and Obtain Compliance

Monitoring should look for most common violations:

- Failed to follow protocol requirements
- Inadequate case histories
- Discrepancies between source records and case report form
- Inadequate drug/device accountability records
- Enrolled ineligible subjects

And Indicators of Fraud

The Protocol Violation Spectrum

Minor

- a missed lab test, a missed visit

Major

- ineligible subject enrolled
- safety or efficacy assessments not done
- did not report serious adverse events to IRB

Significance of Violations

Do the violations

...affect rights, safety, or welfare of subjects?

...directly impact integrity of data set?

...indicate systemic problems within the study = sponsor problems*?*

...indicate problems with the investigator that extend to other studies at that site?

Did the sponsor report the problems to FDA?

Suggestions to Improve Protocol Compliance

- Review and understand the protocol
- Identify any procedures in the protocol that differ from standard practice at your establishment
- Thoroughly train study staff
- Use well-designed study-specific forms for documentation

Suggestions to Improve Protocol Compliance

- Identify study-specific procedures and at what points of the study they are required; develop a plan/schedule

- Perform study-required procedures and visits within the required window
  - A large number of out-of-window procedures/visits may indicate too tight a window or poor planning/scheduling

Suggestions to Improve Protocol Compliance

- Carefully review amendments
- Inform all study personnel of any changes in the amendment
- Track versions of the protocol and use the correct version

Suggestions to Improve Protocol Compliance

- Document all protocol deviations
- Review the deviations for trends
- Trends may indicate re-training or a protocol amendment is necessary
- Use the deviations to develop corrective actions to prevent future occurrence

Ways to Prevent Enrollment of Ineligible Subjects

- Protocol criteria should be clear, not subject to differing interpretations
- Train all study personnel involved in determining eligibility to understand the inclusion and exclusion criteria
- Use a form that lists each criterion to assist during subject assessment

Ways to Prevent Enrollment of Ineligible Subjects

- Do not rely on exemptions from the sponsor
  - If there are numerous exemptions, perhaps the protocol inclusion or exclusion criteria should be revised
  - Sponsor's waiver of entry criterion should be in writing and prospective
  - Consult with IRB for its instructions about waivers

Adequate and Accurate Case Histories

Record keeping errors may be minor, or they might impact the safety or welfare of the subject, impact the study data, or undermine the clinical trial process

Examples:

- extensive or uncorroborated data corrections
- adverse event severity is under-reported to sponsor or IRB
- Adverse events are reported *LATE* to sponsor or IRB

Suggestions to Improve Recordkeeping

- Make sure the staff know how to use the sponsor's computer system and understand the expectations
- Use a consistent format to document all aspects of the subject's evaluation and treatment
- Keep records organized and complete
- Develop a system to track and maintain files

FDA has observed that sponsors and monitors may have conflicting written and verbal instructions for how they want investigators to prepare and maintain case histories, and perform corrections.

Where is the Term "Source Data" Defined?

NOT defined in 21 CFR 312 (investigational drugs) or 812 (investigational devices)

See Nonclinical Laboratory regulations

21 CFR 58.3(k) – "raw data"

21 CFR 58.130(e) – describes how data are to be recorded, corrected, and describes automated systems.

Elements of Documentation Integrity

Attributable

Legible/readable

Contemporaneous

Original

Accurate

Common Informed Consent Problems

Study-specific procedures are performed before informed consent is obtained.

The informed consent discussion is conducted by someone who is not authorized.

What is the IRB's intent for the investigator's signature on the form if another person discusses the study?

What if the investigator signs later?

What is the sponsor's/IRB's expectation for "re-consent" when the consent form is revised?

Clinical Investigator Supervision and Authority

- Verify credentials – is your study coordinator a "nurse" with a only a high school education?

- How will you (CI) supervise the conduct of sub-investigators, particularly if they are located at a distance?

Clinical Investigator Supervision and Authority

- What authority do you have over the personnel assisting in the trial?
- Can you fire a study coordinator or other personnel employed by the sponsor?
- How do you report inadequate performance of a monitor hired by the sponsor?

Inappropriate Delegation to Sub-investigators

Investigator – individual who actually conducts an investigation (i.e., under whose immediate direction the drug is administered or dispensed to subjects.

How can you directly supervise subinvestigators who are working in other states or across the country?

This is a BIG challenge for study coordinators and support staff

Sponsor must ensure that the clinical investigator controls the study

Test Article Accountability

- Records should be sufficient to show:
  - Subjects received proper dose/device
  - Which dose/vial/device was provided to which subject and when
  - Accountability for all investigational product
  - Product was shipped, received, and stored at the proper temperature and conditions

Suggestions for Investigators to Prevent Noncompliance

- BEFORE -

- Understand what you are responsible for...

  .....And get training

- Document the delegation of duties

- Develop forms or checklists to make sure all screening tests and study visit activities are performed...*if not provided by the sponsor*

- Don’t overextend yourself with too many concurrent projects

Suggestions to Prevent Noncompliance

- BEFORE -

- Develop a plan for organizing records
  - Clearly understand what records are to be maintained and how they should be completed
  - Original source data for critical study endpoints
  - Use your site's existing record-keeping system as much as possible, discuss this with the sponsor up front
  - All records should meet the ALCOA test

- Train study staff before the study starts....and train replacements when staff leave

Suggestions to Prevent Noncompliance

- During -

- Track dates when reports are due to the IRB and the sponsor
- Promptly report protocol violations to IRB and sponsor.
- Obtain written approval from the sponsor before you do something that is outside of the protocol
- Verify that delegated duties are performed
- Work with monitors
- Correct small problems before they grow
- Question unusual results

Suggestions to Prevent Noncompliance

- After -

Organize the study records ---

- So non-study staff can find them
- To show what a good job you did
- To fulfill record retention requirements
- For possible FDA inspection

(years later - depending on the sponsor and phase of the research)

Stay Informed to FDA

- Social Media
- Facebook • Twitter • LinkedIn • Podcasts •Webinars • Mobile Apps • YouTube • iTunes
- FDA.gov
- Drug Safety Communications • FDA Listserves • MedWatch Alerts • Safety Labeling Changes (SLCs)
- External Outreach
- Mass Media • Stakeholder Briefings • Consumer, Trade, Professional Groups • Medical Journals

Conclusion

- The Inspector will present credentials and "Notice of Inspection" (FDA Form 482) upon arriving at plant.

- The Inspector will examine production process, look at certain records and collect samples.
- At the conclusion of the inspection, the investigator will discuss with firm's management, any significant findings and concerns; and leave with the management a written report of any conditions or practices, which, in the investigator’s judgment, indicate objectionable conditions, or practices.

Conclusion

- List of "Inspectional Observations," also called an FDA Form 483, can be used by firm's management as a guide for corrective action, since the FDA inspector will not usually recommend specific corrective measures.
- Firm can and should respond to the FDA-483 during the discussion with the inspector.
- In fact, corrective actions or procedural changes that were accomplished immediately in the presence of the inspector are regarded as positive indications of your concern and desire to voluntarily correct discrepancies.

Conclusion

- If firm do not agree with the actions being taken by the FDA or
- If you have a question about the jurisdiction of the agency in a particular matter,
- If FDA takes regulatory action against your firm, you should contact a District Compliance Officer for advice under those circumstances.
- You can contact the FDA's Office of the Ombudsman to seek a resolution.

THANK YOU FOR LISTENING AND WATCHING MY PRESENTATION