Heed the Warnings!

Using FDA Warning Letters to Stay Audit Ready

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Presentation Overview

- Overview of Inspection Process
  - Events Leading Up to Warning Letters
- Accessing/Researching 483s and Warning Letters
- Top Findings in Clinical Investigation Warning Letters
  - Top by number and/or seriousness
  - Preventative Approaches

Events Leading up to Warning Letters
**FDA Inspection Process**

- Who gets inspected?
  - Investigators
  - Sponsors
  - Sponsor-Investigated
  - IRBs
- Types of inspections
  - For Cause
  - Routine
  - Targeted Clinical Investigations Inspections

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**FDA Inspection Requirements**

- Conducted under FDA’s Bioresearch Monitoring Program (BIMO)
- Guide for inspections: Compliance Program Guidance Manuals

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**Steps in Inspection Process**

- Presentation of “Form 482” Notice of Inspection and identification
- Avoid allegations of “refusal” – entry or access to information
- Interview of PI/Research Coordinator
  - PI appearance and participation is not optional
  - List of studies on which PI is investigator or co-investigator
### Additional Items to Consider for Inspection
- Coordination of units that may be inspected/involved
  - IRB
  - Investigational Drug Service
  - Medical records
- Logistics
  - Work space, location of documents, copies, parking
  - On-site assistance from research coordinator
  - Check-in visits/daily briefings

### Steps in Inspection Process
- Inspector review of study documentation including medical records
  - Have documents gathered and ready
  - Copying – copy what inspector copies
  - Arrange for access to electronic systems
- Exit interview
  - Arrange for compliance office to be there
  - And include in-house counsel as necessary

### Steps in Inspection Process
- Exit Interview Outcomes:
  - No findings
  - Verbal review of suggested items
  - Issuance of Form 483 Inspection Observations
  - Voluntary response to Form 483 within 15 business days of issue
    - CAPA
    - Items with which you disagree
    - FDA may issue response letter accepting CAPA and may verify CAPA
Steps In Inspection Process

- Inspector submission of Establishment Inspection Report (EIR)
  - Not everything is listed on the 483
  - Chance of getting a warning letter or other administrative action even if you don't get a 483
- Classification of EIR by District Office/Center and decision as to any Administrative Action
  - No Action Indicated (NAI)
  - Voluntary Action Indicated (VAI)
  - Official Action indicated (OAI)

Administrative Action Types

- Warning Letter – for violations that may lead to enforcement action if not promptly corrected
- Untitled Letter – for less significant violations
- Regulatory meetings, Clinical hold on investigation or termination of IDE
- Rejection of site data
- Consent Agreement
- Disqualification Proceedings

Inspection Process

- Issuance of Warning Letter
- Site Response
  - Response Letter – may or may not be posted
- FDA Review of Site Response
  - FDA must verify the corrective actions in response letter are actually implemented
  - If accepted and verified, Close-Out Letter is issued
  - Close-Out Letter is posted online at FDA website.
Site Response & CAPA is Key to Avoiding Warning Letters

- FROM MULTIPLE WARNING LETTERS:
  
  “Your response is inadequate because it does not contain sufficient detail. Specifically, you did not provide details regarding how you will implement your corrective action plan. Without those details, we are unable to determine whether your corrective action is adequate to prevent similar violations in the future.”

CAPA Should Include:

- Detailed response to each item
- SOPs
- Roles and responsibilities
- Training – materials; audience; completion
- Verification of implementation
- Review/monitoring plan

What’s Worse than a Warning Letter?

- NIDPOE Letter = Notice of Initiation of Disqualification Proceedings & Opportunity to Explain
- Repeatedly or deliberately failed to comply with the requirements for conducting clinical investigation; and/or
- Repeatedly or deliberately submitted false information to FDA or to the sponsor in any required report.
**How Bad Can it Be? It’s Just a Warning – Right ????**

- Reported to sponsors and IRBs
- May result in clinical investigation suspension
- May result in contract cancellation or withdrawal of funding
- May result in follow audits by sponsor, IRBs, other government regulatory or funding agencies (if they didn’t already result from 483!)
- Sponsors will not longer consider investigator for future trials.

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**Accessing and Researching Warning Letters**

- Published? Not usually, but sometimes.
- FDA Office of Regulatory Affairs (ORA) Electronic Reading Room
  - [http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/default.htm](http://www.fda.gov/AboutFDA/CentersOffices/OfficeofGlobalRegulatoryOperationsandPolicy/ORA/ORAElectronicReadingRoom/default.htm)

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**Form 483s**

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What Form 483s Get Published by FDA

- Those selected by FDA at its discretion – published “proactively.”
- Those that are most frequently requested via Freedom of Information Act (FOIA).
- Non-public information redacted.
- BUT listed under name of recipient and site address.

Other Avenues for Accessing 483s

- Freedom of Information Act Request
  - FDA gets over 1,000 FOIA requests for 483s each year
  - May not be released while an investigation is pending
- Commercial Providers
- Non-profit “watchdog” organizations

Accessing Warning Letters

- All warning letters are published online on FDA website: [http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/UCM2005393.htm](http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/UCM2005393.htm)
- Listed by year.
Accessing Warning Letters

- Also listed by FDA unit responsible for enforcement: [http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLettersstoPharmaceuticalCompanies/ucm380323.html#DSI](http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLettersstoPharmaceuticalCompanies/ucm380323.html#DSI)
- Office for Scientific Investigations responsible for clinical investigation warning letters
Accessing Site Responses to Warning Letters

- Site may submit a response letter to a warning letter and ask that it be posted FDA site.
  - Must be provided in electronic format
- FDA may or may not post site response on FDA website.
- “The agency has reserved the right not to post certain responses, such as when posting likely would mislead the public about the safety or efficacy of a regulated product.”

Researching Warning Letters

- Multiple ways to search warning letters
  - By year
  - Company/investigator name
  - Issuing office
  - Subject
  - Warning letters with posted response letters
  - Warning letters with close-out letters
  - Recently published
  - Free text search box
Top Findings in Clinical Investigation Warning Letters and Preventative Approaches

Data Sources for Top Findings

- FDA summarizes inspection observations on an annual basis.
  - [http://www.fda.gov/ICECI/Inspections/ucm250720.htm](http://www.fda.gov/ICECI/Inspections/ucm250720.htm)
- Includes breakdown for 483s issued by BIMO
- Observations listed on 483s translate into regulatory citations listed on warning letters.
- Review of warning letters.
Number 1 Citation in Terms of Volume: Protocol Noncompliance

- "An investigation was not conducted in accordance with the [investigational plan]. Specifically**"
- 21 CFR 312.60

Examples of Failure to Follow Investigational Plan

- Failure to perform protocol-required procedures.
  - Missing safety labs
  - No documentation of reasons participant missed tests, missed visits, etc.
- Failure to ensure eligibility criteria are met by all participants.
- Making changes to protocol without first obtaining IRB approval for reasons other than immediate patient safety.
Prevention

- Train investigators & coordinators on critically reading the protocol.
- Don’t confuse treatment and research!
- Identify differences between what protocol requires and what is typically done in clinic.
- Review protocol deviations — if a deviation occurs more than once, examine root cause.
  - Is a protocol modification in order?
  - Is participant at fault? Document what happened and evaluate if sponsor should be contacted about evaluating further participation.

Prevention

- Monitor sponsor-investigators for impromptu protocol changes.
- Establish eligibility assurance processes.
- Eligibility checklists are great, but not if signatures on them are meaningless.
- Checklist should include reference to medical record that shows where eligibility criteria are confirmed.
- Train on “trust but verify.”

Second Highest Volume Citation: Inadequate Case Histories

- "Failure to prepare or maintain [adequate] [accurate] case histories with respect to [observations and data pertinent to the investigation] [informed consent]. Specifically, ***"  
- 21 CFR 312.62(b)
Examples of Inadequate Case Histories

- Failure to complete case report forms.
- Failure to maintain underlying source documentation to support data recorded in case report forms.
- Failure to document review of lab results.
- Failure to properly document informed consent.
- Lost records.
- Failure to document timely review of adverse event.

One Recent Example

- “Study records contained hypersensitivity assessment forms that were signed and dated but that did not contain any subject identification or any other information with regard to hypersensitivity signs and symptoms.”
- “On September 9, 2013, you sent an e-mail to the sponsor noting that due to the large number of subjects, you signed and stamped the blank forms just prior to filling them out.”
- “In your December 3, 2013, written response, you indicated that you would stamp a block of hypersensitivity forms and indicated that you should have drawn a line across the signed, unused forms and initialed and dated them. You also stated that you plan to avoid this type of practice in future clinical trials. Please note, we expect that you will not pre-sign blank forms in FDA-regulated studies in the future.”

Prevention

- Compare protocol to case report forms to ensure necessary data is captured and source documents capture necessary study data.
- Complete case report forms in real time, not just before the next monitoring visit.
- Require research teams to have regular meetings at which PI reviews case report are with spot-checking against source documentation.
- No blank, investigator pre-signed forms!
- No white-out; no pencil
**Corollary – Record Retention**

- Numerous citations in warning letters for failure to follow record retentions requirements.
- Adequate storage facilities.
  - A box stuffed under the desk or jammed in a store room is just asking to get lost.
- Include record retention responsibilities in clinical trial agreements.
  - How long? Who pays? When can they be returned to sponsor?
  - What if investigator leaves?

**One Recent Example**

- During the inspection, you stated:
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  "[A]ll study related records and source data pertaining to protocol (b)(4) at our site were shredded including, but not limited to, signed informed consent forms, subject diary cards, records of screening results, documentation of assessments at additional study related visits, and laboratory test results. This data is not retrievable and was not available for inspection. Due to the destroyed study records, [the FDA investigator] was not able to verify the study data for protocol (b)(4), or the existence of signed informed consent forms during the inspection."
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- During the inspection, your study coordinator provided Investigator Babbitt with a copy of a Standard Operating Procedure (SOP), signed by you and with an effective date of October 30, 2008, for study-record retention. We are concerned that this SOP appears to be insufficiently detailed to prevent similar violations in future studies. Of note, based on the description you provided during the inspection, the boxes of study records that were shredded were labeled with pertinent identifying study information, such as sponsor, date range of the study, subject numbers, and protocol number. Your SOP for study-record retention does not address how you will ensure that boxes of study records that are appropriately labeled will not be shredded erroneously in the future.

* http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2014/ucm411894.htm

**High Volume and Serious: Informed Consent Violations**

- “Failure to obtain informed consent in accordance with 21 CFR Part 50 from each human subject prior to [drug administration] [conducting study-related tests]. Specifically****
  - 21 CFR 312.60
- PLUS multiple warning letters regarding specific consent violations.
Examples of Informed Consent Citations

- No consent before administration of test article.
- Missing consent forms.
- Participant did not sign AND date consent.
- Most recent IRB approved consent form not used.
- Re-consent not obtained or not timely obtained.
- Consent did not adequately advise of risks or failed to include other required elements of informed consent.
- Inappropriate time period between consent signature and first study procedure.
- Consent of non-English speaking subjects.

Some Notable Examples

Your May 24, 2007 response letter states that it is unclear why Subject 7003 was re-consented on the day of surgery, since the subject signed the English informed consent form on October 23, 2006, seven days prior to surgery. Your response does not address whether this subject was bilingual, and does not explain why this subject was given an English consent form on October 23, 2006 and a Spanish consent form on October 29, 2006.

Prevention

- Study teams should be trained on including note on informed consent process in research record.
  - Who consented?
  - Were questions asked/answered?
  - Time to review with family?
  - Provided signed copy?
- Coordinator checklist should include checking to make sure consent form is current.
- Never date/fill out consent forms in advance.
- Use “Goldilocks Rule” for timing of consent.
- Know IRB rules for non-English speaking subjects consent.
- Make sure all form elements are complete.
  - Page initials, check boxes, etc.
High Volume & Serious: Test Article Accountability

- "Investigational drug disposition records are not adequate with respect to [dates] [quantity] [use by subjects]. Specifically, ***"
- 21 CFR 312.62(a)

Examples of test article accountability citations

- Inadequate records of receipt and disposition.
- Test article inappropriately used outside trial.
- Failure to obtain unused investigational drug from participant and document destruction/return.
- Inadequate documentation of drug storage in conformance with protocol
- Poor documentation regarding drug diaries.
- Failure to follow controlled substances regulations when test article is a controlled substance

One Recent Example

- “For Subject 1398757002:
The Investigational Supplies Inventory Log notes that Container #2592361 was administered on November 21, 2010, but the case report form notes that this container was administered on January 21, 2011.”

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2014/ucm399635.htm
Prevention

- Use centralized investigational drug service with solid SOPs and QA.
- Train on a process for handling pill diaries including participant education, reminders, follow-up contact, mailers for return of drug.
- Added security requirements for Controlled Substances.
- Watch script-writing practices!
  - Name and phone number of prescriber on script.

Safety Reports: Adverse Event Review & Reporting; Reportable Events

- May be lumped under “failure to follow the investigational plan” or “failure to protect rights, welfare and safety of patients.”
- May also be cited under specific reporting regulations.
- Covers adverse events, unanticipated problems, serious and/or continuing noncompliance.

Examples

- Failure to grade and attribute adverse events in accordance with the protocol.
- Failure to report adverse events to sponsor and/or IRB in a timely fashion.
- Conflicts between CRFs and source documents.
- No documentation of reason why evaluation of AE was changed.
- Untimely grading and attribution, e.g., grade them all the day before the monitor arrives.
Prevention

- Training, training, training!
- Real-time review and documentation is essential.
- Very complex compliance area due to super-abundance of requirements.
  - Sponsor
  - IRB
  - FDA & OHRP

Sponsor-Investigator

Specific Citation: Improper Monitoring

- “Failure to ensure proper monitoring of the investigation and failure to ensure that the investigation is conducted in accordance with the general investigational plan and protocols contained in the IND [21 CFR 312.50 and 312.56(a)].”

Examples of Lack of Monitoring

- No monitoring plan.
- No follow-up to ensure correction of monitor’s findings.
- Inadequate monitoring of all investigational sites in multi-site trials.
  - Remote monitoring v. site monitoring
Example of Improper Monitoring

- FDA regulations require that sponsors ensure proper monitoring of clinical investigations and ensure that their clinical investigators conduct the investigations in accordance with the protocols contained in the Investigational New Drug file (IND). Our investigation found that you failed to ensure proper monitoring of Protocol (b)(4), and that you did not ensure that a clinical investigator conducted the investigation in accordance with a protocol contained in the IND. As a result of inadequate monitoring, you did not identify and correct in a timely manner a clinical investigator’s failure to obtain informed consent from subjects, in accordance with FDA regulations: a clinical investigator’s failure to ensure ongoing Institutional Review Board (IRB) approval of the protocol; and a clinical investigator’s failure to administer the dose of investigational drug to subjects, according to their protocol-specified treatment arm.


Prevention

- Review IRB SOPs – ensure that monitoring plans are required for sponsor-investigators.
- Catch things at the contract stage – budget for monitors, CRO.
- Remote monitoring may not be enough.
  - One site visit per year.

Sponsor-Investigators: Failure to Carry out General Responsibilities of Sponsors

- “Failure to [select qualified investigators] [provide investigators with the information needed to conduct the study properly] [ensure proper monitoring of the study] [ensure the study is conducted in accordance with the protocol and/or investigational plan] [ensure that FDA and all investigators are promptly informed of significant new adverse effects or risks]. Specifically, ***”
Sponsor-Investigators have “Re-sponsor-abilities”

- IND/IDE
- Annual reports
- Protocol amendments
- PI Selection/training/financial disclosure/1572 or investigator agreement/CVs
- Monitoring
- Review of all safety reports & data and communication to investigators/IRBs/FDA
- Ensure investigator compliance
- Drug accountability
- Labeling

Prevention

- Catch sponsor-investigator studies at contract and/or IRB review stage.
- Implement program to ensure that PI is aware of re-sponsor-ilities before he/she starts.
- Monitor for filing of annual reports; obtaining CVs, etc.
- Review IRB records to ensure sponsor investigators are obtaining any required IND/IDE.
  - Dietary supplements
  - Approved drugs for new indications.

Super Serious Citation: Failed to personally conduct or supervise investigation

- “You failed to personally conduct or supervise the clinical investigations [21 CFR 312.60].”  **Example:**
- “When you signed the Statement of Investigator (Form FDA 1572) for the above-referenced clinical trials, you agreed to take on the responsibilities of a clinical investigator at your site. Your general responsibilities as a clinical investigator include ensuring that the clinical trials are conducted according to the signed investigator statement, the investigational plan, and applicable regulations; protecting the rights, safety, and welfare of subjects under your care; and ensuring control of drugs under investigation [21 CFR 312.60].”
Example of Failure to Conduct/Supervise

- “By signing Form FDA 1572, you specifically agreed to personally conduct the clinical trial or to supervise those aspects of the trial that you did not personally conduct. While you may delegate certain study tasks to individuals qualified to perform them, as a clinical investigator, you may not delegate your general responsibilities. Our investigation indicates that your supervision of personnel to whom you delegated study tasks was not adequate to ensure that the clinical trials were conducted according to the signed investigator statement, the investigational plan and applicable regulations, and in a manner that protects the rights, safety, and welfare of human subjects.”

Example of Failure to Conduct/Supervise

- “Specifically, you failed to adequately supervise individuals to whom you delegated study tasks. Your failure to adequately supervise the conduct of the studies referenced above led to many of the violations noted in this letter. These violations include, but are not limited to, enrollment of ineligible subjects in Protocols (b)(4) and (b)(4) and failure to take adequate precautions to prevent theft or diversion of the investigational drug (b)(4), a Schedule II controlled substance. Had you provided adequate oversight, you may have been able to prevent many of these violations from occurring.”

Prevention

- Mandatory training for investigators and researcher coordinators on delegation of duties.
- Training should include completion of practice delegation of authority log.
- Key training points:
  - Investigator is always responsible
  - Delegation without training and supervision is recipe for disaster.
  - Blame game will not work with FDA inspector.

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2014/ucm398974.htm
Super Serious Citation: Submitting false data

- “You repeatedly or deliberately submitted to FDA or to the sponsor false information in any required report [312.70(a)].”

Example of False Data

- “Based on the information obtained during the course of the inspection, the FDA has determined that you submitted falsified subject records for three subjects enrolled in your clinical trials. The FDA inspection revealed that all of the subjects you enrolled in Protocol (b)(4) and Protocol (b)(4) were, in fact, study coordinators whom you enrolled under fictitious names.”
  - “a. Protocol (b)(4): You enrolled your study coordinator (b)(6) into the study as Subject 1012 under a fictitious name (DCJ).”

Example of False Data

- “In addition, you signed study records that showed the fictitious name for this subject. (b)(6) completed the following study related documents for himself/herself while falsely claiming to be subject DCJ.”
  - “* Patient medical history questionnaire for the December 3, 2008, visit date.
  - * Screening records for Visit 1 on December 3, 2008.
  - On the same date, you signed the physical examination portion of these records as the physician completing the examination.”

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm295583.htm
Prevention

- Strong monitoring/auditing program
- Comparison of source data to CRF
- Promotion of avenues for reporting research misconduct
  - IRB
  - Compliance Office
  -Anonymous reporting via “hotline”

Super Serious Citation: Failure to protect rights, safety welfare of subjects

- “You failed to ensure the safety and welfare of those under your care by failing to ensure that ***. Specifically ***
- 21 CFR 312.60

Failure to Protect Rights, Safety, Welfare Example

Subject 005 in Protocol GLP112756 was to receive an unscheduled replacement investigational drug, administered via a pen, at Visit 24/Week 16 on September 28, 2011. However, your study coordinator dispensed the wrong pen to the subject. The study coordinator placed a request into the Interactive Voice Response System (IVRS) for a replacement pen that was intended for Subject 006 enrolled in the same protocol, but the coordinator dispensed that pen to Subject 005.

On October 29, 2009, Subject 007 in Protocol GLP112757 received and used the investigational drug pen #5036654 that was assigned to Subject 001 enrolled in a different protocol (Protocol GLP112755).

In your written response to the Form FDA 483, you acknowledged that subjects received the wrong investigational drug pens and indicated that you and your staff take full responsibility for the protocol violations noted above.

https://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2014/ucm406852.htm
Other Examples

- Wrong drug
- Wrong dose
- No informed consent; inappropriate LAR; not following rules re. parent/guardian consent; lack of subject capacity to consent
- Failure to ensure safety labs/pregnancy tests and resulting harm.
- Coercion

Prevention

- Bad things will happen even in the best systems.
- Key is ability to demonstrate that to prevent and to immediately detect and remediate once prevention failed.

Take-Aways

- Use Warning Letters as educational tools – helps defeat the “that could never happen here” attitude.
- Review FDA inspection process with researchers.
  - Establish the importance of “audit readiness.”
- Know your FDA inspectors and get involved in inspection process.
Questions?

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