What You Need to Know to Prepare for an FDA Audit

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Host
Dawn Burke, Product Marketing Manager
Specialized Software by Forte

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Comprehensive clinical research management system for mid-size to large organizations with complex needs.

Cloud-based clinical trial management system that manages the operational data for small to mid-sized sites.

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A Site Insights Dashboard for organizations to compare their performance to that of their peers.
Presented by

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Madeleine Williams, MA, CIP, is a Senior Director in Huron’s Education practice. Maddie has over 12 years of research experience and her specific areas of experience include the management of engagements focused on clinical research compliance, research project management and Institutional Review Board (IRB) operations, structure and function. Maddie’s focus is on helping organizations to improve their processes, enhance research compliance and improve efficiency.
This webinar will cover the following key issues:

- Understanding what may trigger an FDA audit
- Understanding what the FDA will be looking for during an audit
- Common findings of FDA audits
Polling Question #1

What is your biggest concern about being audited by FDA?

A. Won’t have complete documentation; missing files
B. Non-compliance with regulations
C. PI won’t know answers to auditor’s questions
D. All of the above
Triggers for an FDA Audit
What Triggers a GCP Audit

• New Drug Application (Data Validation)
  – 70% of audits are associate with applications
  – May be linked with a sponsor/CRO audit

• Complaints (“For cause” inspection)
  – 30% of audits follow a complaint
  – Complaints are from any source

• Surveillance inspections
  – IRB
  – GLP facilities
FDA Risk Based Approach

- Application level
  - Submission type
  - Population vulnerability
  - Target population size

- Study level
  - Pivotal study
  - Trial Design Type
  - Location of site
Risk Attributes by Site (Clinical Site Level)

- Number of INDs per Site/Investigator
- Financial disclosures
- Site type
- Protocol deviations
- Number of sub-investigators and the location of the sub-investigators (same facility or far away?)
- Principal Investigator complaints
- Time since last inspection
- Geographic distribution of sites and subject populations
Risk Attributes by Site (cont.)

- Enrollment
- Efficacy outcome
- Non-serious adverse events
- SAEs

- Percentage of subject deaths
- Enroll/screen percentage
- Subject discontinuation
Complaint “For Cause” Inspections

• Credible allegation involving significant risk to:
  – Subject rights and/or safety
    • Patient death or significant injury
    • Inadequate subject protection
  – Data quality or integrity
    • Falsification of or unrealistic data
    • Rejection by the sponsor of investigator data
    • Under-reporting or delay in submission of adverse events
    • Inadequate monitoring of clinical investigations
    • Significant financial interest in the product by the investigator

L. Ball (FDA), ACRP 2011
What are the Complaints About?

- Informed Consent Issues
- Falsification
- Failure to report adverse events
- Failure to follow the protocol
- Inadequate Records
- Qualifications of persons performing physicals
- Failure to get IRB approval, report changes in research

- Failure to follow FDA regulations
- Drug accountability
- Recruitment Practices
- Poor Supervision
- No active IND
- Monitoring practices
- Blinding
- Misleading advertisements
What may Prompt an Inspection of Device Clinical Research?

- New product or indication
  - Premarket approval (PMA) or notification (510(k))
- New technology
  - Investigational device exemption (IDE)
- Complaints
  - Allegations of research misconduct
- Non-compliant history
  - Previously violative (OAI) inspection
- Routine surveillance

M. Tarosky, “How to Prepare for a Bio research Monitoring Inspection”, Division of Bio research Monitoring, CDRH, FDA
Polling Question #2

If you have been audited by FDA, what was the reason?

A. Subject complaint or subject injury
B. High enrolling site
C. Other reason
D. Not sure
E. Have not been audited by FDA (yet!)
What FDA Looks for in an Audit
What the FDA Looks For During an Audit

- Obligations of Clinical Investigator
  - Investigator maintains control of the study by appropriate delegation of study tasks to research staff that are qualified by experience and training
  - Investigator follows protocol as approved by the IRB
  - Amendments to protocol approved by IRB prior to implementation except when necessary to eliminate apparent immediate hazard to subjects
What the FDA Looks For During an Audit

• Obligations of Clinical Investigator (Cont.)
  – Appropriate consent process and documentation
    • Consent in language understandable to subjects or LAR
    • Method of consent (in person, telephone, translator used)
    • Consent prior to enrollment or any study-related procedures
    • Each subject or LAR given a signed and dated copy of consent
    • Appropriate version of consent document used
What the FDA Looks For During an Audit

• Source Documentation
  – Study documents organized and complete
  – Case Report Forms
    • Compared with source documents
    • Verify eligibility of enrolled subjects
    • Protocol-specific labs
    • AEs documented and reported
      – Investigator assessed severity and relationship to protocol
What the FDA Looks For During an Audit

• Electronic Records
  – Accurate and complete
  – Suitable for review and copying
  – Meets requirements for paper records - ALCOA
    • Attributable
    • Legible
    • Contemporaneous
    • Original
    • Accurate
What the FDA Looks For During an Audit

• Test Article Control
  – Who is authorized to administer and dispense
  – Supplied only to those authorized to receive
  – Compare amount shipped, received, used, returned or destroyed

• Proper Storage
  • How is it secured
  • Who has access

• Proper Labeling of article
What the FDA Looks For During an Audit

• Study Records
  – Retained according to protocol and regulatory requirements
  – Reports required by sponsor
  – Study monitor reports
  – Follow-up to deficiencies found by monitor
  – Monitoring for sponsor-investigator studies
How to Proactively Prepare for an FDA Audit
FDA Called-Now What?

• Will give you a timeframe for audit
  – Can request a delay
• Gather source documentation
• Alert study staff
• Assign and define inspection roles
  – Host
  – Interviewee
  – Scribe
  – Runner
  – Escort
FDA Called-Now What? (cont.)

• Discuss ground rules with study staff on answering questions, be honest and truthful, etc.
• Find a workspace for the auditor
  – Out of earshot
  – Comfortable
  – Provide a desk
• Document what you provide to the auditor
• Check what the auditor returns
• OK to ask
  – Questions
  – An explanation of the regulatory basis
• Recommended actions
  – Take responsibility (Don’t blame others)
  – Be careful about offering unrequested information
FDA Guidance Investigator Responsibilities
Protecting the Rights, Safety, and Welfare of Study Subjects

• In assessing the adequacy of supervision by an investigator, FDA focuses on four major areas:
  – whether individuals who were delegated tasks were qualified to perform such tasks
  – whether study staff received adequate training on how to conduct the delegated tasks
  – whether there was adequate supervision and involvement in the ongoing conduct of the study, and
  – whether there was adequate supervision or oversight of any third parties involved in the conduct of a study.
Appropriate Delegation

• Screening evaluations, including obtaining medical histories and assessment of inclusion/exclusion criteria, conducted by individuals with adequate medical training

• Evaluation of adverse events by individuals having appropriate medical training, knowledge of the clinical protocol, and knowledge of the investigational product

• Assessments of primary study endpoints by individuals having appropriate medical training and knowledge of the protocol

• Informed consent obtained by individuals with medical training, knowledge of the clinical protocol, familiarity of the investigational product, and ability to discuss the risks and benefits of a clinical trial with prospective subjects
Adequate Supervision

• Routine meetings with staff to review trial progress and update staff on any changes to the protocol or other procedures
• Written materials to ensure appropriate supervision and conduct
Written Materials to Ensure Appropriate Supervision and Conduct

- Job descriptions, training plans, on-the-job training documentation, training records, licenses, CV and resume
- PI supervision, oversight, delegation, staff qualifications for study responsibilities
- Procedural documents (SOPs, forms etc.)
  - Make sure you follow your SOPs
Adequate Training

• Ensure that staff:
  – Have a general familiarity with the study and the protocol
  – Have a specific understanding of the details of the protocol and the investigational product, relevant to the tasks they will be performing
  – Are aware of regulatory requirements and acceptable standards for the conduct of clinical trials, both in respect to conduct of the clinical trial and human subject protection
  – Are competent to perform the tasks that they are delegated
  – Are informed of any pertinent changes during the conduct of the trial and educated or given additional training as appropriate
Ensure High Quality Data and Subject Safety

• Build quality into the conduct of the study
  – Create systems that limit opportunity for errors
  – Simplify protocol and outcomes assessments
  – Standardize systems and formats were possible, use validated instruments/definitions
  – Keep protocol amendments to a minimum and check CRFs and consent forms against each change
  – Insist on training and then test it, do beta tests/dry runs
  – Have a disaster plan, e.g. back ups if key study staff leave or site experiences flood or disaster

L. Ball (FDA), ACRP 2011
Polling Question #3

What would be the most difficult to implement at your site in preparation for an audit?

A. Ensuring appropriate delegation
B. Training all of the staff
C. Ensuring all documentation is complete and accurate
D. Ensuring the PI provides appropriate supervision
E. None of the above/Other
Metrics and Common Findings
Deficiencies Found in FDA Audits
FDA Office of Compliance

- Protocol Non Compliance: 35%
- Poor Record Keeping: 25%
- Poor AE Reporting: 19%
- Poor Drug Accountability: 11%
- FDA Non Compliance: 10%
Who Investigators Believe is Responsible for Compliance Failures

- CRA
- Subinvestigator
- Self
- Sponsor
- CRC/Study Personnel
Example Establishment Inspection Report (EIR)

Summary of Findings

This inspection of a prospective manufacturer of earlier FDA inspection of 7/97. The finished produc was conducted as a follow-up to an

supply the

inspection, several inspectional observations were noted and discussed with the firm.

Immediate corrections were promised by the firm and the purpose of this follow-up was to
determine if suitable corrective actions have indeed been enacted.

This firm will synthesize and

During the 7/97

Credentials were shown and FDA482 issued to Mr. Herbert E. Paaren, Vice President of the
corporation. Mr. Peter O. Johnson, President of the corporation is not present at the firm on a
daily basis and was not present during this inspection. According to Mr. Paaren, he himself is
actually the person most responsible for day to day operations. He added that there have been
no changes to the firm’s ownership, responsible parties or corporate standing since the last
inspection. Also present during this inspection were Christopher M. Henrich, QC, and
Katherine J. Beardsley, Director of Regulatory Affairs. All three of these individuals answered
questions and supplied document copies as requested.

This inspection was limited in scope and covered only the firm’s correction of the previous
FDA483 items.

#1. There is no documentation showing the

the finished product have been validated.

http://www.foiservices.com/brochure/inspectrpts.cfm
Example 483

<table>
<thead>
<tr>
<th>Name of Individual To Whom Report Issued</th>
<th>Period of Inspection</th>
<th>C.F. Number</th>
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<td>Edwin H. Wegman</td>
<td>See below</td>
<td>2424009</td>
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<th>Title of Individual</th>
<th>Type Establishment Inspected</th>
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<tr>
<td>President and Chief Executive Officer</td>
<td>Biological Drug Manufacturer</td>
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<table>
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<tr>
<th>Firm Name</th>
<th>Name of Firm, Branch or Unit Inspected</th>
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<td>Same</td>
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<td>35 Wilbur Street</td>
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<td>Lynbrook, NY 11563</td>
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During an inspection of your firm, we observed:

Out-of-specification lots of Santyl ointment have been released after it was determined the method of calculating potency based on a relationship of standard to sample was in error. The Agency had been advised in July 1999 that the results of the study, “Demonstration of the Equivalence of Laboratory-formulated Standard Collagenase Ointment and Actual Manufactured Standard Collagenase”, approved 7/13-14/99 by Directors of Pharmaceutical Development and Quality Control, and the VP of Quality concluded that “there is no statistically significant difference in the results obtained from laboratory formulated and actual manufactured standard collagenase ointments”. Later studies, conducted as early as January 2000, culminated with the reported conclusion in early June 2000 that historical potency data show that there is 70% recovery of the active in the ointment standard however, a 77% recovery in batches of final product ointment. Despite these findings, no modification to the existing method of determining potencies using the identified conversion factor of 1 was made to SCP #102. Product continued to be released based on the earlier and erroneous comparison of the results of these assays up to and including 7/25/00. From the beginning of June 2000 to July 25, 2000.
This inspection is a part of FDA’s Bioresearch Monitoring Program, which includes inspections designed to evaluate the conduct of FDA-regulated research to ensure that the data are scientifically valid and accurate, and to help ensure that the rights, safety, and welfare of the human subjects of those studies have been protected.

At the conclusion of the inspection, Mr. Martinez, Mr. McClure, and Dr. Klepinger presented and discussed with you Form FDA 483, Inspectional Observations. We acknowledge receipt of your April 5, 2013, written response to the Form FDA 483. We also acknowledge receipt of a progress update from you, dated May 15, 2013, regarding your response to the Form FDA 483.

From our review of the FDA establishment inspection report, the documents submitted with that report, and your April 5, 2013, written response, we conclude that you did not adhere to the applicable statutory requirements and FDA regulations governing the conduct of clinical investigations and the protection of human subjects. We wish to emphasize the following:

1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
2. You failed to protect the rights, safety, and welfare of subjects under your care [21 Cfr 312.60 and 21 CFR 312.305(c)(1)].
3. You failed to obtain informed consent in accordance with the provisions of 21 CFR part 50 [21 CFR 312.60, 21 CFR 50.25(b)(3), and 21 CFR 50.27(b)(1)].
This letter describes the results of a Food and Drug Administration (FDA) inspection that concluded on July 25, 2013. An FDA investigator met with your staff to review your conduct of a clinical study entitled (b)(4). The FDA conducted this inspection under the Bioresearch Monitoring Program, which includes inspections designed to review the conduct of research involving investigational drugs.

At the end of the inspection a Form FDA 483, Inspectional Observations, was issued and discussed with you. We received and reviewed your letter dated August 2, 2013 (“Response Letter”) in response to the Form FDA 483.

Based on our evaluation of the evidence obtained by the FDA, we have determined that you violated regulations governing the proper conduct of clinical studies involving investigational new drugs, as published in Title 21, Code of Federal Regulations (CFR) Part 312 (available at http://www.gpoaccess.gov/cfr/index.html). The applicable provisions of the CFR are cited for each violation listed below.

1. You failed to ensure that the investigation was conducted according to the signed investigator statement, the investigational plan, and the applicable regulations, and to protect the rights, safety, and welfare of subjects under your care. [21 CFR § 312.60].

2. You failed to administer the drug only to subjects under the investigator’s personal supervision or under the supervision of a subinvestigator responsible to the investigator. [21 C.F.R. § 312.61].

3. You failed to prepare and maintain adequate and accurate case histories that recorded all observations and other data pertinent to the investigation on each individual administered the investigational drug. Case histories include case report forms and supporting data. [21 CFR § 312.62(b)].

4. You failed to obtain the informed consent of each human subject to whom the drug was administered in accordance with the provisions of 21 CFR Part 50. [21 CFR § 312.60].
Points To Consider When Responding to a 483

• Take 483s SERIOUSLY
• Accept responsibility as appropriate
• If the letter is inaccurate, explain why and provide specific documentation to support the explanation
• Indicate a clear understanding of the scope and root cause of the problem
Generally Not Persuasive to FDA

- Not sending a response to 483 or WL
- Vague or general responses to violations
- Blaming 3rd parties for deficiencies
- Asserting that another regulatory authority had different findings
- Referencing audit certificates of another sponsor
- Absence or loss of records (due to hurricanes, floods, fires, etc.)
Negative Implications of an FDA Audit

- Site shutdown
- PI Disqualification
- Bad publicity
- Legal Issues
Questions?
Thank you

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• Compliance/regulatory
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