The FDA is Here - From Verbal Observations to Warning Letters

University of Miami
Office of Research Compliance and Quality Assurance

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Research Compliance and Quality Assurance
Research Compliance and Quality Assurance

- Resides within The Office of the Vice Provost for Research and reports directly to the Vice Provost for Research
- Close working relationship with the Human Subject Research Office (HSRO), the Institutional Review Board (IRB) and other operational departments, but independent from those functions
- RCQA provides the following university-wide functions: Good Clinical Practice (GCP) auditing; assistance with federal audits before, during and after the inspection; Research Compliance related education; Clinical Trial Disclosure (CTD) support and oversight; Corrective and Preventive Action (CAPA) plan support and oversight
Objectives

- Define causes for the issuance of FDA Warning Letters (WL)
- Define the significance of WLs
- Analyze the different component of WLs
- Define potential consequences of WLs
- Develop strategies to avoid WLs
- Examples of Notice of Initiation of Disqualification Proceedings and Opportunity to Explain (NIDPOE)
Abbreviations and Definitions

- CAPA – Corrective Action Preventive Action
- CI – Clinical Investigator
- FDA – Food and Drug Administration
- FOIA – Freedom of Information Act
- GCP – Good Clinical Practice
- GMP – Good Manufacturing Practice
- IC – Informed Consent
- IP – Investigational Product
- IRB – Institutional Review Board
- NIDPOE - Notice of Initiation Of Disqualification Proceedings And Opportunity To Explain
- RCQA – Research Compliance and Quality Assurance
- UL – Untitled Letter
- WL – Warning Letter
What is the Form FDA 483?

- The Form FDA 483 informs the Principal Investigator (Institution) in writing of significant objectionable conditions observed during an FDA inspection.

- Verbal Observations: observations made by the FDA Investigator during the exit meeting. In general, those comments should be addressed in writing if a Form FDA 483 is issued. Those observations will be included in the FDA Investigator’s report to the agency.
What are objectionable conditions?

Objectionable conditions are observations identified by an FDA investigator during an inspection. Usually, those observations will be listed on the Form FDA 483, accompanied by applicable citations from the Code of Federal Regulations (CFR).
What is an FDA Warning Letter

"...a correspondence that notifies regulated industry about violations that FDA has documented during its inspections or investigations. Typically, a Warning Letter notifies a responsible individual or firm that the Agency considers one or more products, practices, processes, or other activities to be in violation of the Federal Food, Drug, and Cosmetic Act (the Act), its implementing regulations and other federal statutes. Warning Letters should only be issued for violations of regulatory significance, i.e., those that may actually lead to an enforcement action if the documented violations are not promptly and adequately corrected. A Warning Letter is one of the Agency’s principal means of achieving prompt voluntary compliance with the Act."
What is a Untitled Letter?

- FDA uses Warning Letters for violations that may lead to enforcement action if they are not promptly and adequately corrected.

- FDA uses Untitled Letters for violations that are not as significant as those that trigger warning letters. Unlike a Warning Letter, an Untitled Letter does not include a statement warning that failure to promptly correct a violation may result in an enforcement action.

http://www.fda.gov/AboutFDA/Transparency/TransparencyInitiative/ucm284105.htm
Responses to Form FDA 483, Warning Letters and Untitled Letters

- Form FDA 483: within 15 business days
- Warning Letter: within 15 business days for GCP; 10 business days for GMP inspections
- Untitled Letter: within 15 business days
- Respond to FDA within 15 business days and include objective evidence as applicable
- FDA will generally know within 60-seconds if you “get it”*
- FDA expects a mix of short-term and long-term remediation activities and a timeline for long-term commitments

*“We know within 60 seconds or less if you get it or not.” (former FDA CDRH chief, Tim Ulatowski, December 2006)

For more information in regards to responses to the FDA, please attend related RCQA classes.
Form FDA 483 Responses
Triggering WLs

You can be sure to receive a WL if your Form FDA 483 response includes any of the following. Note: these are actual quotes from WLs:

• You cited us on a technicality
• This was the fault of a research coordinator
• The protocol had rules that weren’t scientifically based so we didn’t feel the need to follow
• We got verbal approval
• Too much paperwork and fine print to follow
• The data set was too complicated to do a full analyses
• As to the forged signatures, those 4 were within an acceptable statistical margin of error given the number of documents your inspector looked at
• We maintain everything in email and your investigators refused to spend the time [for 18,000+ emails] necessary to review
Review of Warning Letters

Issued to: Weiner, MD, Miami Gardens (former Cetero Research, July 2014)
Role: Clinical Investigator (for 1 year)

Observations:

- You failed to ensure that the investigation was conducted according to the investigational plan [21CFR312.60].
- You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21CFR312.62{b}].
Review of Warning Letters

Issued to: Weiner, MD (cont.)

Details of Observations:

- Hypersensitivity assessment forms not completed for 55 reviewed subjects prior to dosing
- Hypersensitivity assessment forms not completed for the day following the dosing day
- Subject 037 was a cousin of a study staff and subject 004 was the son of a study staff member (exclusion criteria).
- Signs and symptoms of hypersensitivity (tachycardia, nausea) not recorded
- Missing hypersensitivity forms
Issued to: Weiner, MD (cont.)

Details of Observations:
- Signed and dated blank forms containing no other documentation in study records. Email to sponsor noted that due to the large number of subjects, blank forms are signed and dated “just prior to filling them out.”
- Telemetry records were missing for 27 out of 38 subject reviewed for inclusion.
- Electrocardiograms missing
Review of Warning Letters

Issued to: Weiner, MD (cont.)

Responses from CI (2013):
- CI stated that he had no access to study records at the time of response and did not recall that any of the assessments were not performed; hypersensitivity assessment forms were completed and any adverse reactions were captured as an adverse event. CI stated that he was not able to review inclusion/exclusion criteria information and did not recall issues with enrollment of relatives. CI indicated in response that subjects experiencing tachycardia had these symptoms prior to dosing and their heart rates later returned to normal. Finally, he stated that it “does not appear logical to conduct the assessments on some of the patients and only part or none on others.” He stated that he should have drawn a blank line on forms signed and dated and he will avoid this practice in the future.
Review of Warning Letters

Issued to: Weiner, MD (cont.)

Outcome:
FDA stated that at a preliminary discussion during the audit, the CI was officered copies of the study records, which he declined. Each part of the CI response was deemed inadequate since CI did not include actions to prevent similar violations in the future. Responses were deemed inadequate since no documentation was included to provide proof of statements; no explanation for missing study records.

“Your failure to maintain adequate and accurate case histories, including the failure to record signs and symptoms of hypersensitivity and the failure to maintain telemetry records and electrocardiograms, compromise the validity and integrity of data captured at your site and raises concerns about the adequacy of your protection of study subjects enrolled at your site.”
Review of Warning Letters

Issued to: Weiner, MD (cont.)

Discussion points:
- What were the major issues here?
- What is the significance of these observations?
- What are potential consequences of this WL?
- What went wrong in his response to the FDA?
- Could this WL have been avoided? If so, how?
Review of Warning Letters

Additional WLs from 2014:

Wise, MD:
Shredded all records for two research studies

Outcome:
“…Failure to retain study records as required by FDA regulations compromises the validity and integrity of data significantly. Because you failed to retain drug accountability records and case histories for both studies, we consider the data generated at your site for Protocols . . Unreliable in support of a research or marketing application.”
Review of Warning Letters

Additional WLs from 2014:

Sewell, MD:
- Ineligible subjects enrolled
- Visits out of window
- Incorrect dosing
- Incorrect PK sampling
- Lack of SAE reporting
- Study procedures not completed
- Inadequate case histories (late changes [3 years] without indicating a reason for changes)
- AEs not recorded
- Inadequate records of the disposition of IP (dates, quantity, use by subjects); contradicting information in regards to dispensation and return of IP
Review of Warning Letters

Additional WLs from 2014:

Sewell, MD cont.:
Outcome:
• Inadequate response- no statements in respect to own corrective actions; no training documentation of CI and staff;
• Response in regards to inclusion criteria insufficient (“professional opinion of CI”)
• No details provided in response
• No SOPs provided

“…Failure to perform protocol-required assessment and procedures and failure to conduct study visits within the protocol specified time frames jeopardize subject safety and data integrity…Your failure to maintain adequate and accurate case histories, including the failure to document a rationale for changes in adverse event classification and in the assessment of adverse events relationship to the study drug, jeopardizes subject safety and welfare and compromises the validity and integrity of data capture at your site…”
Review of Warning Letters

Additional WLs from 2014:
Birhiray, MD:

- Failure to adhere to investigational plan – IP not stopped;
- SAEs not reported
- Failed to perform study procedures as per protocol
- Failure to maintain adequate and accurate case histories – “yes” or “no” responses not provided appropriately to questions if subjects consent to participate in optional future research; two discrepant ICFs

Outcome:
Response was inadequate since CI did not provide corrective and preventive actions; adequate plan for training CI and staff not included; lack of actions as to prevention of future protocol violations;

“…Your failure to document informed consent properly, raises concerns about the extent to which subjects’ rights were protected at your site…”
NIDPOE

Notice Of Initiation Of Disqualification Proceedings And Opportunity To Explain

• A NIDPOE letter informs the recipient clinical investigator that FDA is initiating an administrative proceeding to determine whether the clinical investigator should be disqualified from receiving investigational products. Generally, FDA issues a NIDPOE letter when it believes it has evidence that the clinical investigator repeatedly or deliberately violated FDA's regulations governing the proper conduct of clinical studies involving investigational products or submitted false information to the sponsor.

• The FDA has the authority to disqualify researchers from conducting clinical testing of new drugs and devices, when the agency determines that the researcher has repeatedly or deliberately not followed the rules intended to protect study subjects and ensure data integrity.

• The agency may also ban, or “debar” from the drug industry individuals and companies convicted of certain felonies or misdemeanors related to drug products. Debarred individuals may no longer work for anyone with an approved or pending drug product application at FDA. Debarred companies may no longer submit abbreviated drug applications.
Based on our evaluation of information obtained by FDA, we believe that you have repeatedly or deliberately submitted false information to the sponsor or FDA in required replies, and repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products, as published under Title 21, Code of Federal Regulations (CFR), part 312.

This letter provides you with written notice of the matters complained of and initiates an administrative proceeding, described below, to determine whether you should be disqualified from eligibility to receive test articles as set forth under 21 CFR 312.70, and disqualified from eligibility to conduct any clinical investigation that supports an application for a research or marketing permit for products regulated by FDA.
Dr. Bernard A. Corbett III, M.D. cont.

• You repeatedly or deliberately submitted to the FDA or to the sponsor false information in any required report [21 CFR 312.70].
• You falsified records by signing them to indicate, falsely, that you had performed study-related activities that were actually done by others while you worked elsewhere.
• You admitted signing your name to study records for examinations that you did not perform. Specifically, you stated the following in your affidavit: “I have signed patient examination records, including injection site inspections . . . although I did not see the patients. The patients’ records that I was told to sign would be left in a folder on my desk and I would come in after hours and sign them. I cannot remember the number of records that I signed under those circumstances.”
• You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60].
• Enrollment of subjects who do not meet eligibility criteria jeopardizes subject safety and welfare, and raises concern about the validity and integrity of the data collected at your site.
• Allowing a treatment assignment to be disclosed to a study staff member who is not permitted to have that information also raises concerns about the validity and integrity of the data collected at your site, because study staff members were not blinded to the subject’s treatment arm.
Dr. Bernard A. Corbett III, M.D. cont.

• You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation on each individual administered the investigational drug or employed as a control in the investigation [21 CFR 312.62(b)].

• You have not documented why these weights were changed in the study records. Your failure to maintain adequate and accurate case histories, including the failure to maintain accurate weight measurements on Subject 108-009, compromises the validity and integrity of data captured at your site.
On the basis of the above-listed violations, FDA asserts that you have failed to protect the rights, safety, and welfare of subjects under your care; repeatedly or deliberately submitted false information to the sponsor; and repeatedly or deliberately failed to comply with the cited regulations, thereby placing unnecessary risks to human subjects and jeopardizing the integrity of data, and the FDA proposes that you be disqualified as a clinical investigator. You may reply to the above-stated findings, including an explanation of why you should not be disqualified as a clinical investigator, in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR 312.70.
Dr. Bernard A. Corbett III, M.D. cont.

Discussion points:
- What were the major issues here?
- What is the significance of these observations?
- What are potential consequences of this NIDPOE?
- Could this NIDPOE have been avoided? If so, how?
References


Preparing for FDA Clinical Investigator Inspections; http://www.fda.gov/training/CDRHLearn/ucm180878.htm


External Audits for Research Policy, HSR-P-002, University of Miami

http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/
Upcoming RCQA Classes

In December, we will inform you about the upcoming classes for 2015 and we will also offer several additional classes (Informed Consent, Good Documentation Practice, Protocol Compliance, etc.) for our social behavioral researchers at the Coral Gables campus.

Sign-up for these classes is as always via ULearn.

RCQA Class Schedule

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<th>Date</th>
<th>Time</th>
<th>Location</th>
<th>Campus</th>
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<tr>
<td>Introduction and Overview of Clinical Trial Disclosure</td>
<td>7-Nov</td>
<td>3:00pm - 4:30pm</td>
<td>DT-12 Lrg Conf room</td>
<td>Medical</td>
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<tr>
<td>Report Reporting on clinicaltrials.gov</td>
<td>13-Nov</td>
<td>12:00pm - 4:00pm</td>
<td>Calder Library B014</td>
<td>Medical</td>
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<td>Warning Letters</td>
<td>14-Nov</td>
<td>10:00am - 11:00am</td>
<td>DT-12 Lrg Conf room</td>
<td>Medical</td>
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<td>Preparation for an FDA Audit</td>
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<td>2:30pm - 3:30pm</td>
<td>DT-12 Lrg Conf room</td>
<td>Medical</td>
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<td>Responding to Form FDA 483</td>
<td>11-Dec</td>
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<td>DT-12 Lrg Conf room</td>
<td>Medical</td>
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<td>Warning Letters</td>
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<td>Medical</td>
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Questions?
How to Contact us

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To make an anonymous report, visit the Cane Watch webpage: