

FDA Inspections, 483's & Warning Letters

How to Avoid and Survive Them

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Outline

- Overview
- FDA Inspection Process
- Case Studies from FDA 483s & Warning Letters
 - Clinical Investigators
 - IRBs

FDA Authority

- Authority derived from 21 CFR 312, 812
- Biomedical Research Monitoring Programming (BIMO), established in 1977
- Objectives
 - To protect the rights, safety, and welfare of subjects involved in FDA-regulated clinical trials;
 - To verify the quality and integrity of the research data
 - To assess compliance with FDA's regulations governing the conduct of clinical trials.

BIMO Inspections



- Inspection assignments issued by Center to District Office
- Types of inspections
 - Routine/Surveillance
 - For Cause
- Announced vs. unannounced inspections
- Compliance Programs
 - Clinical Investigators
 - Institutional Review Boards
 - Sponsors, Monitors & Contract Research Organization
 - In-vivo Bioequivalence facilities
 - Good Laboratory Practice (Non-Clinical Laboratories)

Why would you be inspected?

- Routine inspection:
 - Clinical Investigator - verify data submitted to the FDA
 - FDA is interested in what you're doing
 - IRB: Every 5 years
- For-cause/Directed
 - FDA receives information that calls into question study conduct or IRB practices
 - Can be limited to one area of concern or cover entire study/compliance program

FDA Inspection: What not to do





Inspections, Compliance, Enforcement, and Criminal Investigations

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Bioresearch Monitoring

Compliance Program Guidance Manual For FDA Staff

Compliance Program 7348.811 Bioresearch Monitoring: Clinical Investigators

December 8, 2008

Cover page	Cover Page
Part I	Background
Part II	Implementation
Part III	Inspectional
Part IV	Analytical
Part V	Regulatory/Administrative
Part VI	References and Program Contact
Part VII	Headquarters' Responsibilities

Preparing for the Inspection



FOUNDED BY BRIGHAM AND WOMEN'S HOSPITAL
AND MASSACHUSETTS GENERAL HOSPITAL

**Research Compliance Standard Operating Procedure (SOP) and Guidance:
Coordination of FDA Clinical Investigator and Sponsor-Investigator Inspections**

- Finalized August 2014
- Provides information to Investigators and staff regarding FDA Inspection process and required written response
- Applies to any FDA Inspection of a Clinical Investigator or Sponsor Investigator
- RM Portal: Resources > Research Compliance > Audits & Inspections
 - <https://partnershealthcare.sharepoint.com/sites/phrmResources/c/ai/Documents/FDA%20Inspection%20Standard%20Operation%20Procedures.pdf>

Preparing for the Inspection

Partners FDA Inspection Guidance - 2

- Assigns roles for involved parties during FDA Inspection
 - PI is the main point of contact for FDA; referred to as the Designated Official
 - Institutional Liaison (IL) is the person designated by institution to serve as point person to the Investigator
 - Responsibilities include: monitor progress of inspection, inform institutional leadership, coordinate key aspects of any written response
 - IL can be present at all significant interviews and meetings with the FDA, as allowed
 - Additional roles include: Directors of the PHRC/IRB, Directors of Research Compliance, Hospital Sr. VP for Research

Preparing for the Inspection

Partners FDA Inspection Guidance -3

- FDA Inspection support = Collaborative Effort
 - Ensures Investigator is prepared and connected to institution throughout inspection
 - Ensures necessary PCRO/Grants & Contracts/Sponsor reporting
 - Ensures institution is well informed about regulatory deficiencies/observations made by FDA

Preparing for the Inspection



- Document the call to schedule the inspection and any subsequent conversations with FDA
- Notify study staff, Sponsor, IL, and Partners Human Research Committee
- Review and organize study documentation
 - Comprehensiveness, accuracy, and compliance
 - Correct what can be corrected
 - QI Program can help!

On Inspection Day

- Have available:
 - Personnel knowledgeable about all aspects of study
 - A quiet area to conduct inspection with access to internet and a photocopier
 - All study documents
 - Access to electronic records, if applicable
 - Standard operating procedures

On Inspection Day

- FDA Personnel will:
 - Present credentials
 - Issue Form FDA 482 (Notice of Inspection)
 - Interview PI and study personnel
 - This is an in-depth interview about the study – **PI should be familiar with study protocol and documents**
 - Review study documentation



During the Inspection

- FDA inspector will verify:
 - The degree of delegation of authority
 - Who performed various aspects of the protocol (eligibility, consenting, etc)
 - How were study staff oriented/trained on the protocol and investigational product
 - That the PI followed the study protocol approved by the IRB
 - Where specific aspects of the protocol were performed
 - How and where data was recorded

During the Inspection

- You should:
 - Answer questions to the best of your knowledge
 - Request summary of any inspectional findings be provided at end of each day
 - Keep study team up to speed
 - Make a shadow copy of anything FDA copies
 - Have someone taking notes at meetings
- You should not:
 - Sign anything without legal counsel
 - Make an educated guess or provide opinion of something you were not involved in

End of Inspection

- FDA Investigator will conduct an exit meeting with PI and study team
 - IL can attend if needed/wanted
- Issue Form FDA 483 – Inspectional Observations for significant deviations from the regulations, *if any*
 - Make sure you understand the detailed observations that are associated with each observation!
 - 483 is not a final FDA determination!

FDA Form 483

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION	
DISTRICT ADDRESS AND PHONE NUMBER 22201 23rd Drive SE Bothell, WA 98021-4421 (425) 486-8788 Fax:(425) 483-4996 Industry Information: www.fda.gov/oc/industry	DATE(S) OF INSPECTION 11/17/2009 - 11/20/2009 FEI NUMBER 3010692
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED TO: Mr. Paul Newell, Plant Manager	
FIRM NAME Willamette Shelling Inc	STREET ADDRESS 14975 NE Tangen Rd
CITY, STATE, ZIP CODE, COUNTRY Newberg, OR 97132-6856	TYPE ESTABLISHMENT INSPECTED Hazelnut Processor
<p>This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.</p>	
DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:	
OBSERVATION 1	

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE Jinkee M. Vila Binayug, Investigator <i>JM Vila</i> Graham N. Giesen, Investigator <i>G N Giesen</i> Jeffrey J. Leclair, Investigator <i>J J Leclair</i>	DATE ISSUED 11/20/2009	
	FORM FDA 483 (09/98)	PREVIOUS EDITION OBSOLETE	INSPECTIONAL OBSERVATIONS

Back at FDA – New England offices

- FDA Inspector completes Establishment Inspection Report (EIR)
- EIR, FDA 483 (if issued), supporting documentation, and preliminary district classification is forwarded to FDA Central

The FDA recommends that
you provide a written
response to form 483

We think it is absolutely
critical that you respond

Back at Your Office

- Respond to form 483 within 15 business days
 - It will be taken into consideration prior to FDA action
 - IL, IRB, and OGC will help draft this response
- The response to form 483 should do the following:
 - Address each specific finding, point-by-point
 - What is the extent? Isolated event or systematic problem?
 - Assessment of root cause
 - Describe the corrective actions (what, when, how)
 - Describe how you will prevent it in the future
 - Timeframe for training
 - Provide any tools or written documentation of staff training
 - Be cooperative, not combative

FDA Actions

- FDA Center evaluates the report and determines final classification for the inspection
- No action indicated (NAI)
- Voluntary Action Indicated (VAI)
- Official Action Indicated (OAI)
 - Warning letter
 - Disqualification (NIDPOE)
 - Rejection of Data
 - Monetary fines
 - Injunction or prosecution



Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

WARNING LETTER

**CERTIFIED MAIL
RETURN RECEIPT REQUESTED**

Ref: 10-HFD-45-09-05

Thomas O'Barr, Jr., M.D.
1431 White Circle NW
Marietta, GA 30066

Dear Dr. O'Barr:

Between September 16 and 30, 2009, Ms. Stephanie Hubbard, representing the Food and Drug Administration (FDA), conducted an investigation and met with you to review your conduct of the following clinical investigations of the investigational drug **(b)(4)**, performed for **(b)(4)**:

Warning Letter

- Issued for violations which are of regulatory significance
- An *advisory*, but does not commit FDA to taking enforcement action
- Failure to adequately and promptly respond to the warning letter may result in regulatory action without further notice

Warning Letters are public!

<https://www.fda.gov/iceci/enforcementactions/WarningLetters/default.htm>

Summary

FDA form 483

- Detailed observations from inspection
 - Subject ID, adverse event, dosing dates, study staff action



Investigator response

- Within 15 days and describes:
 - Extent of problem, root cause of problem, corrective action, preventive action, training, supporting documentation



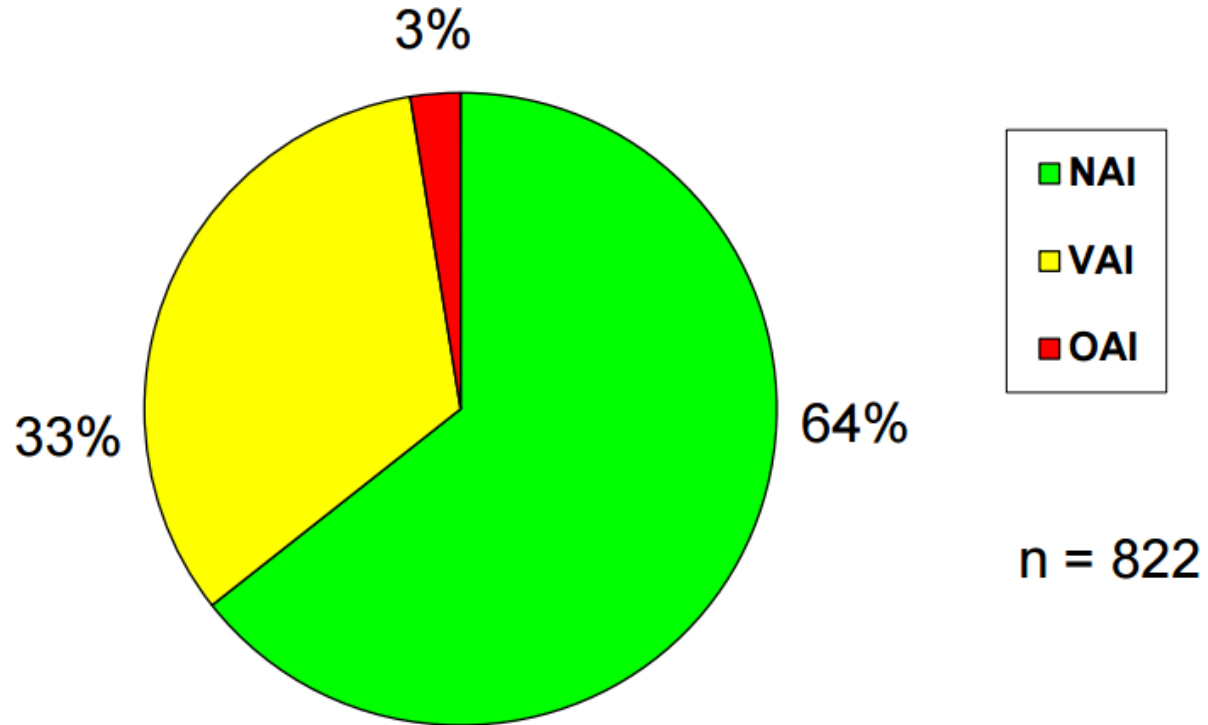
FDA warning letter:

- Cites failure to adhere to federal regulations
- Summarizes issue, provides examples
- Public!

*We shall now drive these points home
with some metrics and case studies...*



FY'15 CI Inspections Classified*



*Inspections classified in FY'15 by all Centers including CVM. Some inspections may have occurred in a different FY.

Most Common CI Deficiencies

- Failure to follow the investigational plan and/or regulations
- Protocol deviations
- Inadequate recordkeeping
- Inadequate accountability for the investigational product
- Inadequate communication with the IRB
- Inadequate subject protection – failure to report AEs and informed consent issues

Excerpts from a January 2017 Warning Letter

Phase 4, randomized, double blind smoking cessation study

1. You failed to ensure that the investigation was conducted according to the investigational plan [21 CFR 312.60]

- Three subjects enrolled (in the past month) that did not meet basic inclusion criteria (ave # cigarettes smoked/day)
- Subject enrolled that had chronic indication excluded from protocol

Excerpts from a January 2017 Warning Letter

Phase 4, randomized, double blind smoking cessation study

2. You failed to maintain adequate and accurate case histories that record all observations and other data pertinent to the investigation ...[21 CFR 312.62(b)]

- For three subjects, diagnosis summary score form not completed; however eCRF section is completed and indicates determination was made based on source score sheet

Excerpts from a January 2017 Warning Letter

Phase 4, randomized, double blind smoking cessation study

3. You failed to maintain adequate records of the disposition of the drug, including dates, quantity, and use by subjects [21 CFR 312.62(a)]

- For two subjects, the amount of drug dispensed at the weekly visit does not match the amount of drug taken, according to the eCRFs. In addition, the amount of drug returned to the site does not match the amount of drug that should have been returned, based on the reported drug dosing records

Example:

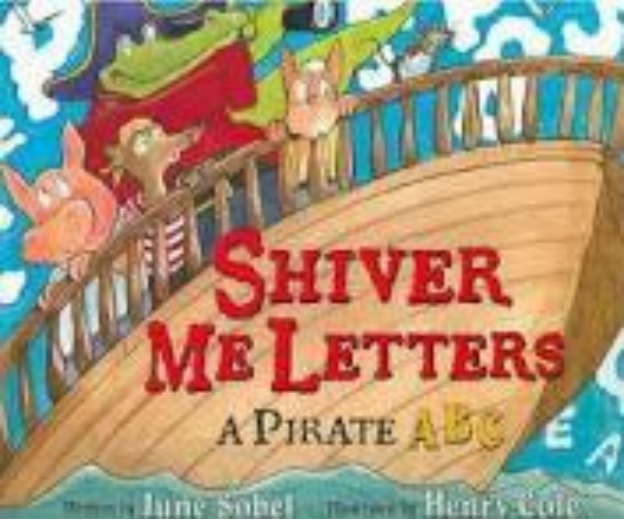
Visit 8/ Weeks 9-10	Drug Dispensed	Drug Taken	Calculated return per reported dosing	Returned to Site
Drug 1	40	44	-4	10
Drug 2	40	44	-4	10
Patch	20	22	-2	5

Excerpts from a January 2017 Warning Letter

Phase 4, randomized, double blind smoking cessation study

FDA RESPONSE:

“We are unable to undertake an informed evaluation of your written response because you did not include any corrective actions that **you, as a clinical investigator**, have taken to prevent similar violations in the future. We are concerned that the majority of corrective actions appear to represent actions taken by [the Sponsor] and **do not reflect corrective actions that you personally have taken**..... you did not provide details on how you personally plan to prevent similar violations in any future studies you may conduct ...



A few additional letters...

Elizabeth L. Hohmann MD
Physician Director, Partners IRBs

Warning Letter 2008 to: Medical Center, Georgia

- **Failure to conduct continuing review of research at least annually [21 CFR 56.109(f)].**
- **Failure to ensure that the IRB reviews proposed research at convened meetings at which a majority of the members are present, including one member whose primary concerns are in nonscientific areas [21 CFR 56.108(c)].**

Actual issues

- Study approved end of March 2008 and first CR conducted June 1 2009.
- Inaccurate attendance records
 - IRB Rosters without degrees/relationship to institution
 - 2 sets of minutes not available (over ~6yrs!)
- Policies and procedures not in place.
- [Remediation underway but inadequate]

Avoided by:

- Our meetings don't start, if quorum not met, and they stop if quorum is lost.
- Detailed updated rosters.
- Detailed voting records.
- C of I recusals are important.
- Complete manual of policies which **MUST** be followed – you can see it on line (or come to a meeting as an observer!).
- No exceptions to 1 year continuing review interval! (continues next slide).

Continuing review

- We cannot grant “extensions;” get your materials in, 45 days in advance of expiry!
- In the event it does lapse, you can continue to see ONLY subjects already enrolled if it is in their best medical interest.

Drug treatment.

Safety F/U of any kind.

Scan scheduled.... Maybe.

Lapsed approval

- Note to request ongoing f/u should include:
 1. Study title, PI, Number
 2. # subjects this applies to
 3. Why it's in their best medical interest to continue
(don't make me guess!)
 4. State in writing that you'll not enroll/screen new subjects until CR is completed/finalized.

Warning Letter, 2009

Oncology MD, Pennsylvania

- You failed to ensure that the investigation was conducted according to study plan...
- You failed to report all changes to the study to the IRS [sic!!]...
- You failed to monitor the progress of the investigation...

Actual issues



- TNTC eligibility/safety tests omitted.
- MD states in response (paraphrased...) – “these weren’t medically necessary so I elected not to” = YIKES!
- Failed to notify IRB of any changes made- i.e. exceptions or violations with rationale
- PI supervising 37 active clinical trials concurrently – FDA apparently doubted he was up to the job.....roles and responsibilities were not clear.

Avoided by - 1



- Describe in your file – roles and responsibilities.
 - Study coordinator (BA)**
 - Educate subjects who call on phone with script/talking points
 - Screen subjects on phone, completing questionnaire (written)
 - Arrange appointments.
 - Phlebotomy
 - Check labs and review with MD any out of range test values.
 - Laboratory assays/QC
 - Review study progress with MD weekly.
 - Visit hospitalized subjects daily and report temps, RN charted data to MD
 - Process payments
 - Complete all IRB and regulatory paperwork and review with MD/PI
 - Perform cultures and specimen processing.
 - **NB: DOCUMENT team meetings!**

Avoided by - 2

- Proper education of investigators.
- GCP training advisable
 - Partners GCP course next spring again!
- Learn from your monitors
 - But beware: they can be of varying quality
 - If no findings, you are not perfect, they stink!
 - 2 recent cases of this.
- Seek assistance from QI Program or IRB.



Other issues found

- Backdating records
- Filling out forms retro- or pro-spectively
- No weights, calculations of dosing, but rather “eyeballing it.”
- People not named on the study doing it.
- Outright forgery.
- Be advised their reach is pervasive – they can move to the IRB, Pharmacy, etc. if they find a problem with YOU!

In Sum...

- Be prepared!
- If you say you're going to do it, you (and we) need to do it.
- FDA coming : Notify the IRB and QI = get help!
- Understand the approach, perspective and procedures of the FDA.
- PI's: Don't accept low work standards from colleagues and employees – you'll live to regret that, I guarantee.
- Don't take it personally.....

References

- FDA Warning Letters:
<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/default.htm>
- FDA Bioresearch Monitoring (BIMO) Metrics FY'11:
<http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RunningClinicalTrials/UCM296250.pdf>
- QI Program: <http://www.partners.org/phsqi/>
- IRB Guidance: see esp. Investigator responsibilities
<http://healthcare.partners.org/phsirb/guidance.htm>
- FDA guidance – Clinical Investigator Responsibilities:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM187772.pdf>